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The American Journal of Medicine

Vol. XIII NOVEMBER, 1952 No. 5

THE MOUNT SINAI HOSPITAL—100th ANNIVERSARY

Introduction

Reprints of Historical Interest

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NEW

prompt... prolonged... prescribed relief of pain

APAMIDE

BRAND • TRADEMARK

tablets

(N-acetyl-p-aminophenol, 0.3 Gm.)

analgesic-antipyretic

rapid, direct analgesia

Apamide quickly relieves pain and reduces fever through direct analgesic-antipyretic action. It avoids the delay inherent in compounds that require metabolic transformation to produce analgesia.

prolonged relief of pain

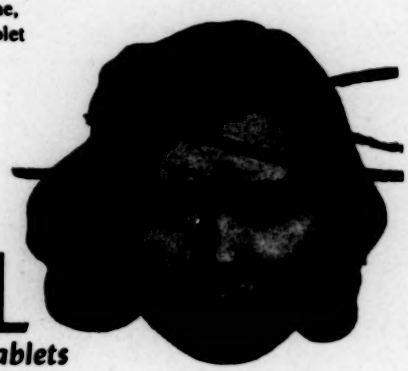
Apamide goes to work fast. It raises the pain threshold substantially within 30 minutes, reaches peak effect in about 2½ hours and continues to be effective for approximately 4 hours.

well-tolerated analgesic

Apamide is a pure, active agent that does not produce extraneous, possibly toxic metabolites. High dosages over long periods have not been shown to cause toxic reactions or gastric upsets. It is extremely valuable in patients who cannot tolerate salicylates.

℞ *only*

Available only on your prescription, *Apamide* permits precise control of dosage and duration of treatment *by you*. Prescribe it for relief of pain and reduction of fever in respiratory infections, functional headache, muscular or joint pain and dysmenorrhea. Average adult dose, 1 tablet every four hours.



for a sedative-analgesic prescribe

APROMAL

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tablets

(N-acetyl-p-aminophenol, 0.15 Gm. and acetylcarbromal, 0.15 Gm.)

non-narcotic, non-barbiturate

Apromal is especially valuable in those cases where pain coexists with tension, anxiety, restlessness, excitement, nervousness and irritability. *Apromal* contains Apamide and the widely used, gentle daytime sedative, acetylcarbromal. Enhancement of both analgesia and sedation is secured by this combination. Average adult dose, 1 tablet every 4 hours.

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Ames Company of Canada, Ltd., Toronto

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The American Journal of Medicine

Vol. XIII NOVEMBER, 1952 No. 5

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The November, 1951, issue of The American Journal of Medicine was dedicated to the bicentennial of the Pennsylvania Hospital; this issue is dedicated to the centennial of The Mount Sinai Hospital of New York. Dr. George Baehr, until recently Chief of the First Medical Service and Director of Clinical Research of the Hospital, serves as Guest Editor for the occasion. In a foreword Dr. Baehr outlines the problems faced by the Hospital in its efforts to keep abreast of trends in the evolution of medicine during the past hundred years, problems common to all progressive hospitals and medical schools throughout this period, and describes the efforts made to meet those problems. Next, Dr. Eli Moschcowitz, who also has served the Hospital with distinction for many years, gives a general account of the founding and early days of the Hospital. Then follow reprints of twelve articles representing noteworthy contributions to medicine made by members of the Hospital Staff. These articles are not mere memorials, of interest only in retrospect. They are worth careful study, as are all primary sources, for their content, their attention to significant detail, their style, their revelation of mind and personality.

An illuminating review of thirty-three cases of Cushing's syndrome, coupled with an analysis of 189 cases culled from the literature. The findings are of special current interest, particularly in regard to the nature of the underlying abnormalities of the adrenal glands, the clinical and laboratory observations, the diversity of complications and the limitations of treatment. Experience with ACTH adds interest to the case analysis, and vice versa.

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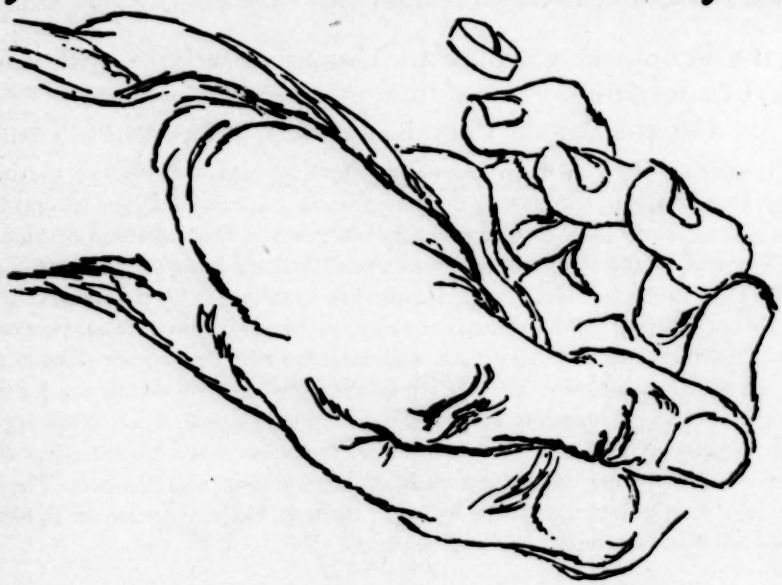
oral penicillin t.i.d.

. . . for the more common bacterial infectious diseases



Just 1 or 2 Pentids Tablets t.i.d. are particularly effective . . . convenient, easy-to-take . . . cause fewer side effects . . . and are less than ½ the cost of the newer antibiotics.

Bottles of 12 and 100.

formulated for convenient t.i.d. dosage **Pentids**

Squibb 200,000 Unit Penicillin Tablets

SQUIBB

CONTENTS

The American Journal of Medicine

Vol. XIII NOVEMBER, 1952 No. 5

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Seminars on Gastrointestinal Physiology

Research Society Abstracts

Case Report

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.

2 highly effective oral dosage forms

BICILLIN*

BENZETHACIL

DIBENZYLETHYLENEDIAMINE DIPENICILLIN G

- Extremely well tolerated
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- Free from unpleasant penicillin taste
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- Dosage schedules need not be influenced by meal times

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...is unusually effective and palatable; ideal for use where flexibility of dosage is desired, as in pediatric practice.

Supplied: bottles of 2 fl. oz., containing 300,000 units per teaspoonful (5 cc.)

TABLETS

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arthritis, bursitis, sacroiliac strain and other rheumatic conditions

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DOSAGE: one teaspoonful elixir or 2 or 3 tablets every 3 or 4 hours; preferably given p.c.

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Sodium Salicylate	125 mg.	400 mg.
Homatropine Methylbromide	1.25 mg.	2.5 mg.
	in each tablet	in each teaspoonful (4 cc.)

samples **and literature on request**

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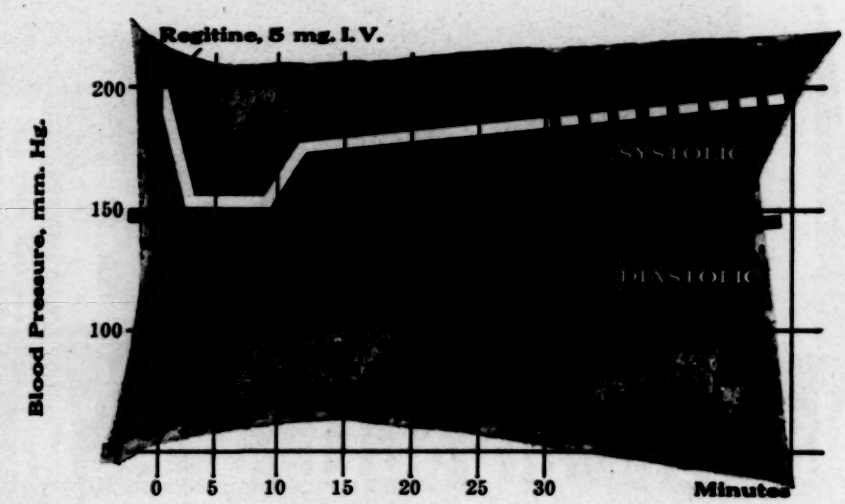
causes

one curable form of hypertension



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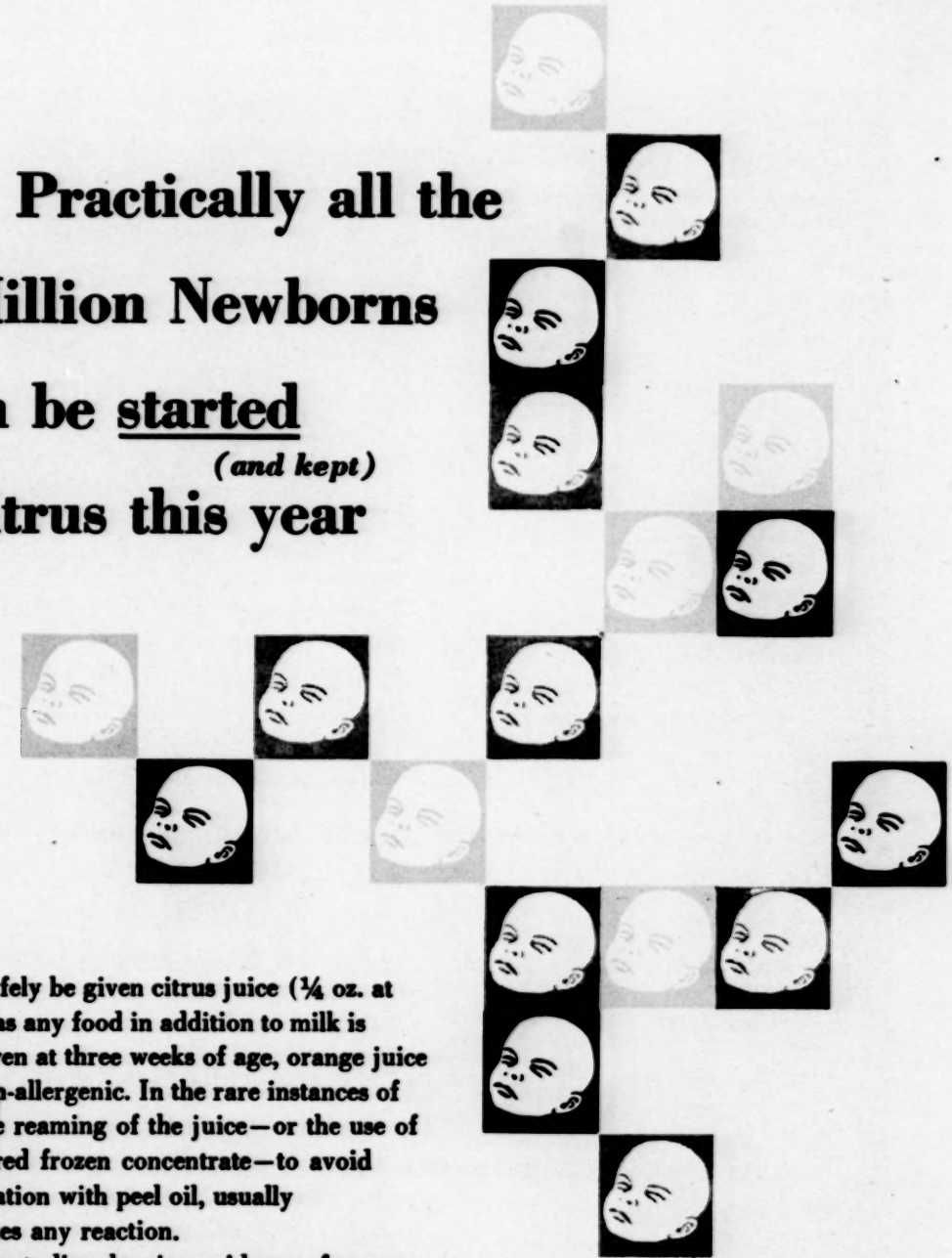

Newborns can safely be given citrus juice (¼ oz. at first) as soon as any food in addition to milk is permitted. Even at three weeks of age, orange juice is virtually non-allergenic. In the rare instances of sensitivity, gentle reaming of the juice—or the use of specially prepared frozen concentrate—to avoid contamination with peel oil, usually obviates any reaction.

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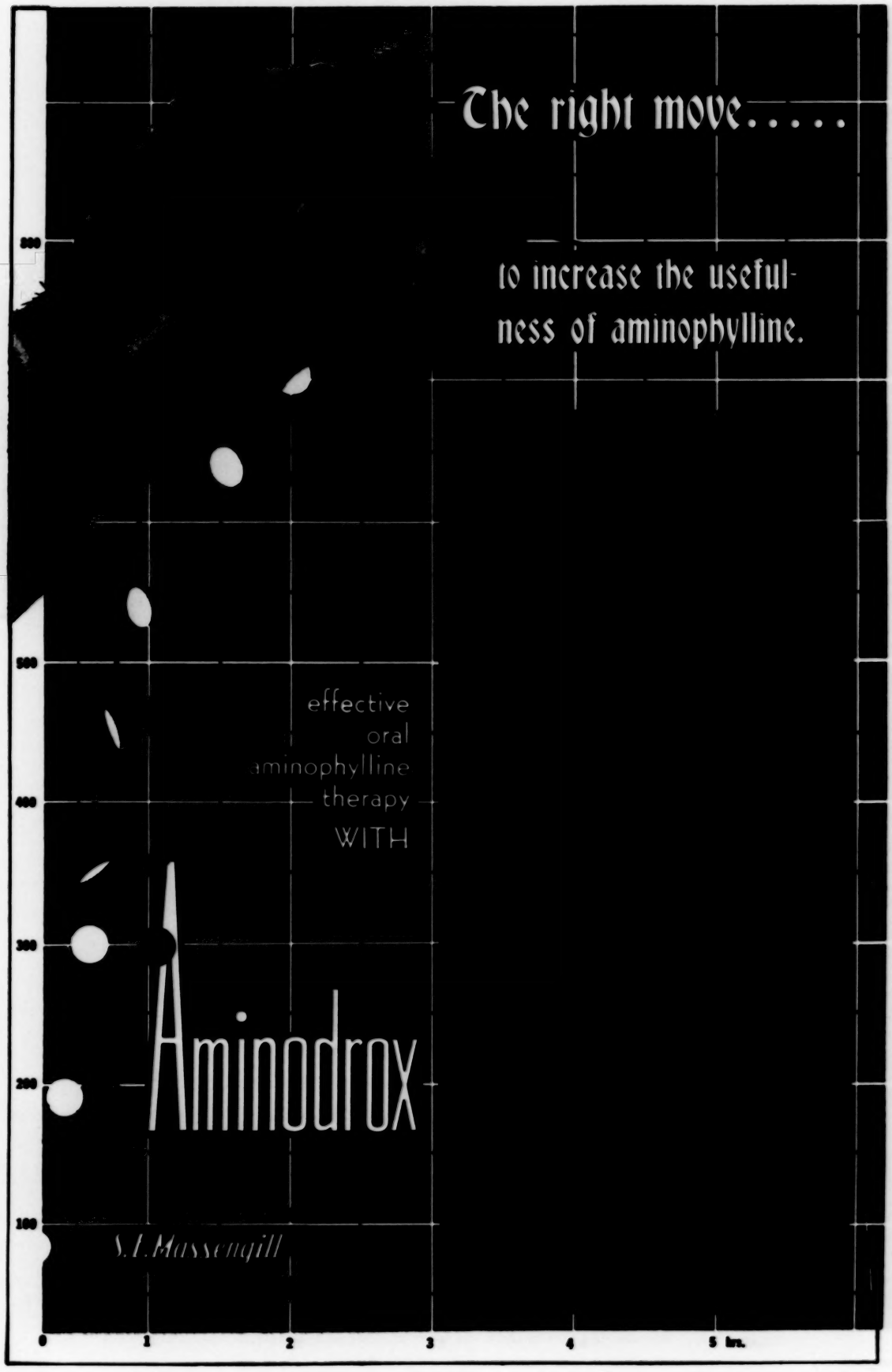
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400
300
200
100
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1
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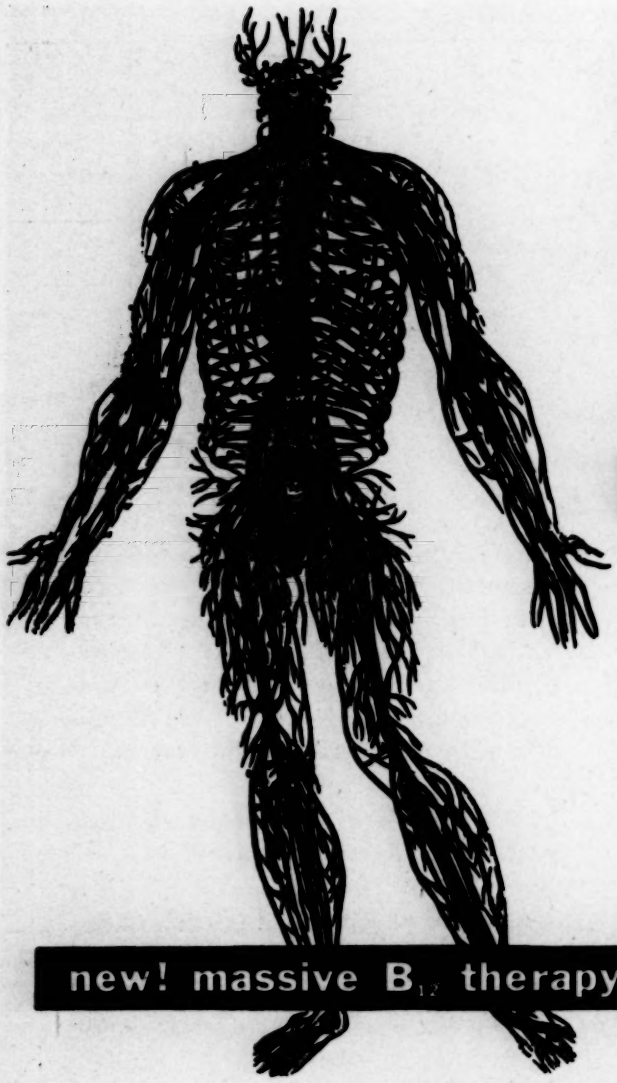
3
4
5 hrs.



dramatic,
sustained relief
in
severe

nerve pain

of

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- diabetic neuritis
- subacute combined sclerosis (of pernicious anemia)
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for intramuscular or subcutaneous injection

Complete or long-time remission of pain in a substantial number of patients • often successful where all other therapy has failed • non-toxic • well worth trying in these disabling, agonizing pain conditions which so often leave the physician so helpless and the patient so hopeless.

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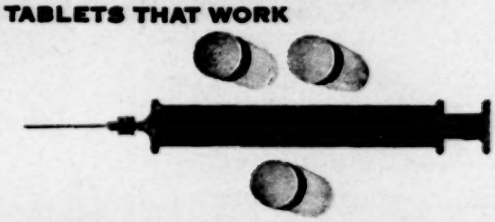
THE DIURETIC TABLETS THAT WORK



PRESCRIBE NEOHYDRIN, when indicated, in congestive heart failure, recurring edema, cardiac asthma, hypertensive heart disease, dyspnea of cardiac origin, arteriosclerotic heart disease, fluid retention masked by obesity and for patients averse to their low-salt diet.

How to use this new drug: Maintenance of the edema-free state has been accomplished with as little as one NEOHYDRIN Tablet a day. Often this dosage of NEOHYDRIN will obtain in a week an effect comparable to a weekly injection of MERCUHYDRIN®. When more intensive therapy is required one tablet or more three times daily may be prescribed as determined by the physician.

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1. Behrman, H. T., Combes, F. C., Bobroff, A., Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
2. Turell, R.: New York St. J. M. 50:2282, 1950.
3. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives Pediat. 68:382, 1951.

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Hamblen, E. C.: North Carolina M. J. 7:533 (Oct.) 1946.

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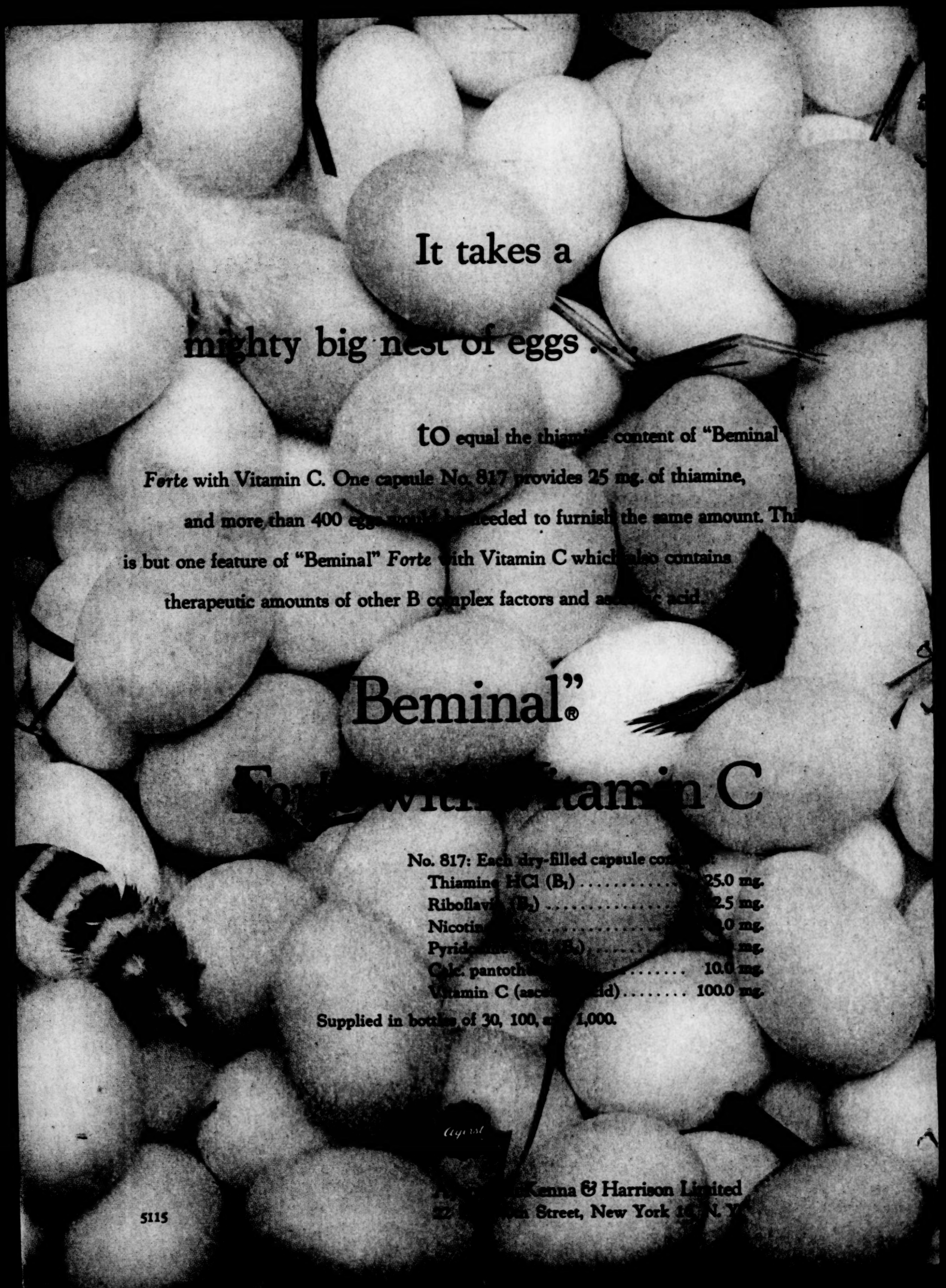
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in ARTHRITIS
and allied disorders

BUTAZOLIDIN

New...
Non-Hormonal...
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for relief of pain plus improvement of function

Now available on prescription, BUTAZOLIDIN is a new and potent agent that has yielded outstandingly favorable results in arthritis and other painful musculoskeletal disorders.

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- *Produces therapeutic benefit* in virtually all forms of arthritis and allied disorders such as bursitis and fibrositis.
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*U. S. PAT. NO. 2,562,830

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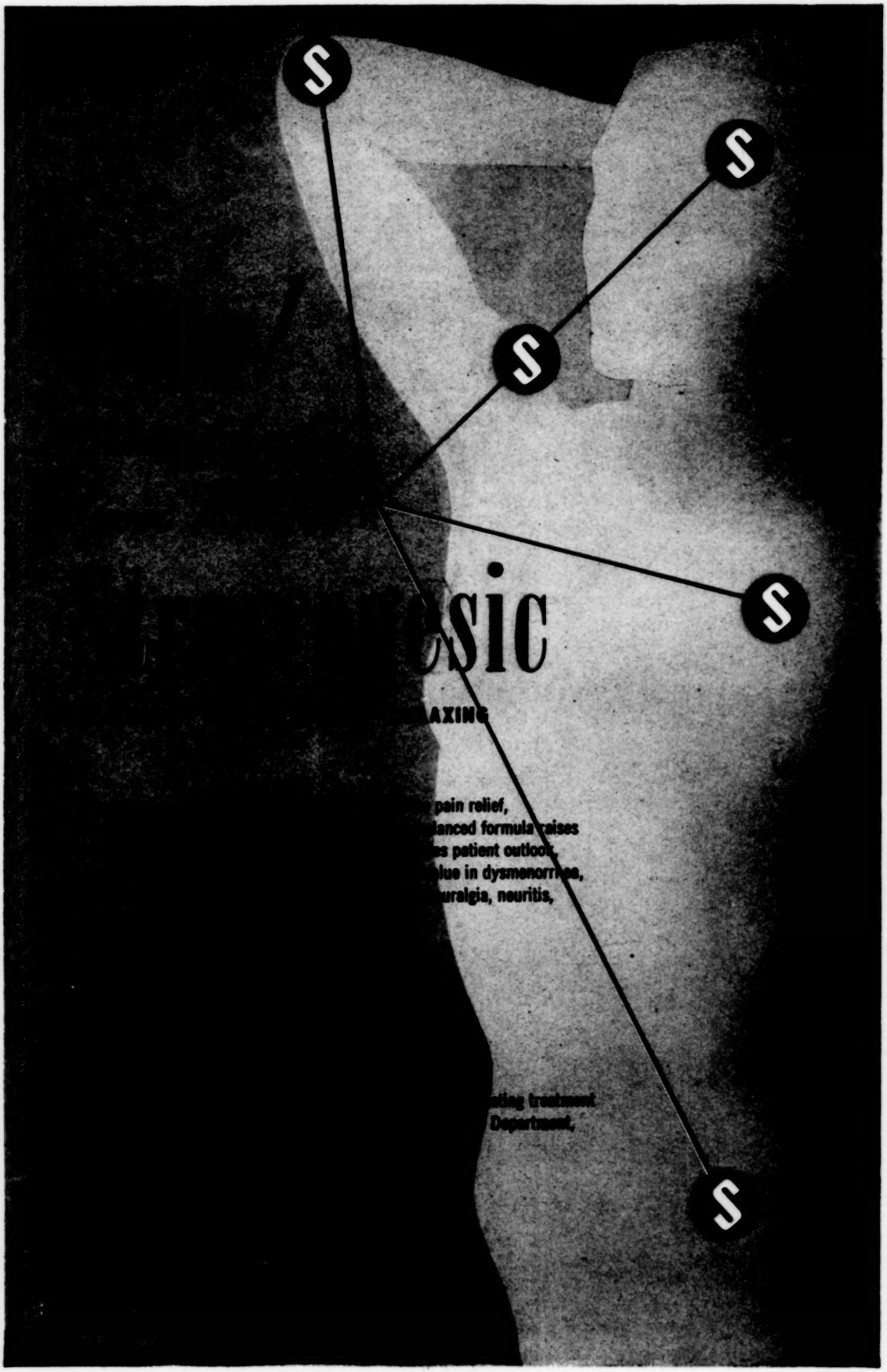
4. Kuzell, W. C., and Schaffarzick, R. W.: Phenylbutazone (Butazolidin) and Butapyrin in Arthritis and Gout. Paper read before the California Medical Association Meeting in Los Angeles, April 29, 1952.

Geigy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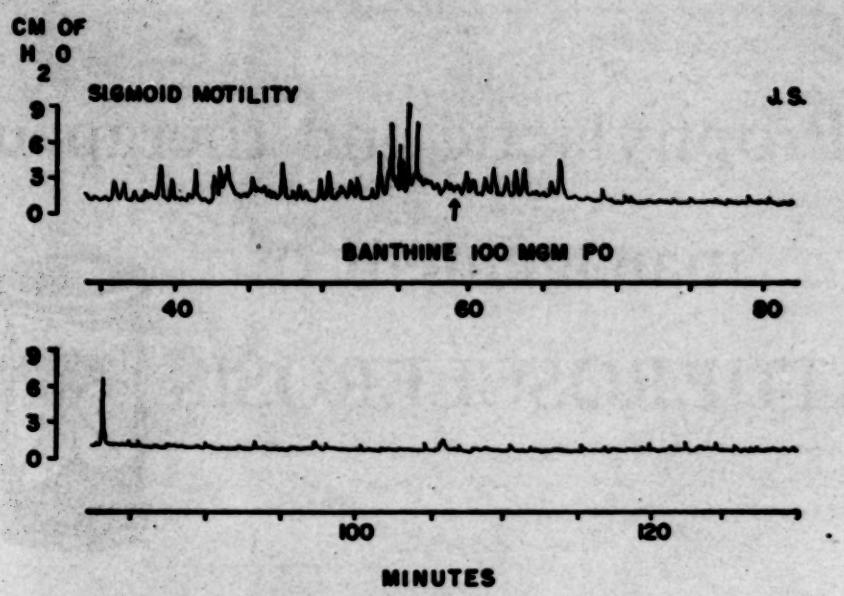

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1. Kern, F., Jr.; Almy, T. P., and Stolk, N. J.: Effects of Certain Antispasmodic Drugs on the Intact Human Colon, with Special Reference to Banthine (β-Diethylaminoethyl Xanthene-9-Carboxylate Methobromide), Am. J. Med. *11*:67 (July) 1951.

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in similar dosage."

Tufts Med. J.,
19:15-19, 1952

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Sodium

The importance of MERCUHYDRIN Sodium in relieving the "drowning" heart has made it a fulcrum of the therapeutic regime in acute or severe congestive failure. In pulmonary edema or paroxysmal nocturnal dyspnea, the prompt, effective action of MERCUHYDRIN may be a life-saving measure, as demonstrated by extensive clinical experience.

Unexcelled for draining edematous tissues, well tolerated locally and systemically, MERCUHYDRIN is an agent of choice for initiating diuretic therapy.

MERCUHYDRIN Sodium (brand of meralluride sodium) is available in 1-cc. and 2-cc. ampuls and 10-cc. vials.

Leadership in diuretic research
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NEW! Relay Action in One Tablet . . .

You can now prescribe immediate-acting, sublingual aludrine (n-isopropylarterenol HCl) *and* the classic theophylline-ephedrine-phenobarbital anti-asthmatic triad in a single tablet. The asthma patient simply places a *Nephenalin* tablet under the tongue until the purple sugar coating is dissolved, then swallows the nucleus.

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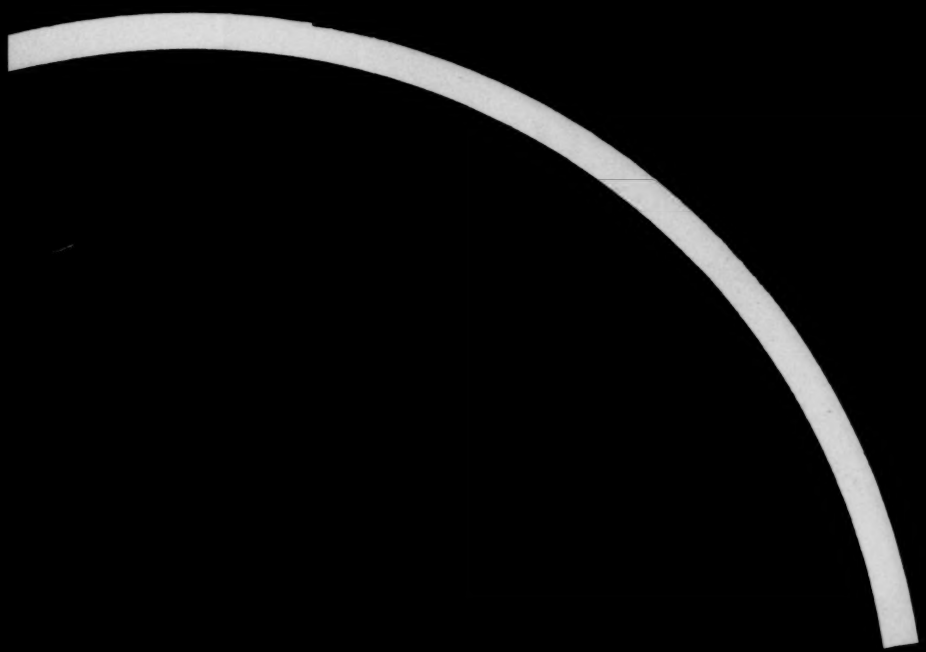

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The American Journal of Medicine

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Introduction

Foreword

THIS issue is dedicated to the men who over the course of a century laid the foundation for the clinical reputation of The Mount Sinai Hospital of New York in the medical world. Some of their contributions to the advancement of medicine are of sufficient historical importance to warrant republication on this centennial occasion. Because of space limitations it has been necessary to omit many papers of equal merit by other members of the Hospital Staff. Among these may be mentioned Henry Koplik's description of the "Koplik spots" in measles (1896); Bernard Sachs' studies, in 1896, on amaurotic family idiocy ("Tay-Sachs disease"); Reuben Ottenberg's discovery of the hereditary nature of the blood groups and related topics, begun in 1908; Fred S. Mandlebaum's comprehensive investigation of the histopathology of Gaucher's disease (1916); the first exposition of the principles of vectorcardiography by Hubert Mann (1920); Louis Gross' studies on the circulation of the heart and heart valves, begun in 1921; the "Libman-Sacks" type of verrucous endocarditis (1924); the initial description of spongioblastoma of the brain by Joseph H. Globus and Israel Strauss (1924); publication in 1925 of "Thoracic Surgery," first American textbook on this subject, by Howard Lilienthal, pioneer in this field; Gregory Shwartzman's discovery of the phenomenon universally known by his name (1928); the early work on female sex hormones by Robert T. Frank and Morris A. Goldberger (1928); introduction of intravenous pyelography by Moses Swick (1929); Paul Klemperer's studies, over a span of two decades, on the pathology of disseminated lupus erythematosus, culminating in the concept of the "collagen" diseases; Sheppard Siegel's initial description of benign paroxysmal peritonitis (1945).

A consistent level of scientific output by any hospital over so long a period depends as much upon the spirit of inquiry within the institution as upon the basic training and abilities of its professional staff. Scientific alertness and inquiry must be bred from within. It may therefore be revealing if we look back a moment upon the early influences and the personalities which created this environment.

At the beginning of its history and throughout the first half century of its existence, the reputation of the Hospital was essentially a reflection of the clinical repute of a distinguished staff of outstanding physicians who had in the first instance been selected by a wise lay board of the Hospital from the medical schools and teaching hospitals of the city; a few were outstanding men who had migrated from European centers of medical learning to establish their careers in the more liberal environment of the New World. Thus, very early, a high level of practice was set in surgery by such men as Valentine Mott and his son, A. B. Mott, Willard Parker, John A. Wyeth and Arpad Gerster; in pediatrics by Abraham Jacobi and Henry Koplik; in ophthalmology by Karl Koller and Charles May; and in medicine by the great clinician Edward Gamaliel Janeway. These men and others like them constituted the vanguard of clinical practitioners and teachers of the day.

In 1852 the basic medical sciences were most rudimentary. Nevertheless, clinicians and surgeons of that era were able to uncover some of the early mysteries of clinical diagnosis by meticulous observation. Perhaps in the absence of the modern instruments of precision their clinical acumen became sharpened, quite like the highly developed sensory perceptions and keener powers of apprehension of the blind.

To this early influence must be attributed the emphasis on problems of clinical diagnosis upon which the reputation of the Hospital was built during the succeeding decades. It can be recognized in the contributions of the first crop of young physicians who developed within the institution itself toward the end of the nineteenth and the beginning of the twentieth centuries, men such as Bernard Sachs, Nathan E. Brill

and Emanuel Libman, whose names are associated in medical literature with the clinical conditions which they described.

Clinical surgery also flourished during that period under the same stimulating influences. The surgical pioneers who developed within the institution during this renaissance included such men as Charles A. Elsberg, one of the founders of neurologic surgery, Howard Lilienthal and Alexis Moschcowitz in thoracic surgery, Albert A. Berg in the modern surgery of the gastrointestinal tract, and Edwin Beer and Leo Buerger, who made substantial contributions in the field of genitourinary surgery.

By the time the first intern training program was established at the Hospital toward the end of the nineteenth century, the rapidly developing sciences of pathology, bacteriology and biochemistry were providing a new foundation for clinical medicine. Upon completing their in-hospital training many of the young physicians of that period journeyed to the great European centers of learning. Upon their return they established the beginnings of the new scientific disciplines in primitive laboratories in the Hospital. At first with little or no material assistance, they labored at great personal sacrifice to develop and keep abreast of the exciting advances in the newly developing medical sciences. They indoctrinated others on the staff; they taught the young interns and sent them abroad to bring back more of the new knowledge and technics. They persuaded the trustees and administrators of the Hospital to improve the physical facilities of the crude laboratories and to provide financial assistance to young physicians through fellowship grants designed to enable them to devote additional years at the Hospital or abroad to basic training in the medical sciences as the foundation for a future career in clinical practice or clinical research. By far the greatest force in this direction was Emanuel Libman.

The clinical productivity of the Hospital during this period cannot be ascribed solely to the fact that clinical "nuggets" were lying on the ground waiting to be picked up by the alert prospector. The important work of that period was based on supporting laboratory data. In fact, the Hospital's clinical productivity during that period can be attributed to the fact that those who did the work of the laboratories were also the clinicians. The scientific laboratories were an integral part of the clinical services.

This first "golden era" of clinical investigation had to end, for by 1926 the laboratories of the Hospital had grown to such size and scope that they required full-time experts in each of the basic medical sciences for their direction. Although relieved thereafter of routine laboratory responsibilities by the appointment of full-time laboratory chiefs, many members of the clinical staff continued to carry on research in the central laboratories or in special laboratory facilities that they developed adjacent to the wards. The dichotomy between the clinical and the laboratory divisions nevertheless had its effect upon the trend of clinical research. Under their new full-time leadership the laboratories became increasingly productive whereas the clinical members of the staff began to experience increasing difficulty in salvaging enough time from private practice and routine ward duties to participate consistently in problems of clinical research, which were becoming ever more complex. This was due only in part to the physical separation of the central laboratories from the clinical services. The major untoward factor was the absence of full-time direction on the clinical services of the Hospital. It gradually became obvious that without full-time leadership the clinical services would inevitably lose ground as the basic medical sciences and their rapidly multiplying subdivisions assumed increasing importance for present-day clinical medicine.

In 1944 the Hospital therefore charted a new course and embarked upon a program of full-time direction of its major clinical departments —at first by the appointment of full-time chiefs for its two medical divisions. Then followed progressively the appointment of full-time chiefs in psychiatry, pediatrics, obstetrics-gynecology and surgery. This cannot help but enhance the educational and scientific program of the clinical services and improve the opportunities for professional and scientific development of the younger members of the staff. As the clinical and laboratory staffs must share many of the physical facilities for research, they are brought together into a close working relationship in which they share their knowledge and their personnel in ever closer collaboration. In this way, it is hoped, a favorable environment has been re-established for clinical investigation and practice, in tune with the rapid progress of the times in which we live.

GEORGE BAEHR, M.D.
7 *East* 12 *Street, N. Y. C.*

Founding and Early Days of The Mount Sinai Hospital*

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ONE hundred years ago, on January 5, 1852, the Jews Hospital in New York, since 1866 known as The Mount Sinai Hospital of the City of New York, was incorporated. The record of incorporation, written in a fine Spencerian hand, is still preserved. It reads, in part, "We, Sampson Simson, Samuel M. Isaacs, John I. Hart, Benjamin Nathan, John M. Davies, Henry Hendricks, Theodore I. Seixas, Isaac Phillips and John D. Phillips, Citizens of the United States of America and the State of New York and Residents of the City of New York, County of New York and State aforesaid, being each over twenty one years of age and desirous of associating ourselves with such persons as may hereafter be admitted as members for benevolent, charitable and scientific purposes in conformity with and under the provisions of an act of the State of New York entitled 'an Act for the incorporation of benevolent, charitable and scientific, and missionary Societies,' passed April 12, 1848, Certify that We have associated and hereby do associate ourselves into a benevolent, charitable and scientific Society to be known and distinguished in law, or otherwise by the name of 'The Jews Hospital in New York,' that the particular business, purpose and object of such association and Society will be Medical and Surgical aid to persons of Jewish persuasion; and for all other purposes appertaining to Hospitals and Dispensaries."

In 1852 Millard Fillmore was President of the United States which was still experiencing the growing pains of the industrial revolution. Our seemingly endless resources were being tapped as never before: mines were being opened, forests felled, new acres planted. Factories were buzzing with activity. The vast distances of our land were being conquered by a network of railways. American clippers were sailing the seven seas, new cities were springing up and old cities were spreading. Gold, which had been discovered a few years previously in a domain recently acquired from Mexico, was luring hordes of men from farms, counting houses and factories to make the trek to the distant bonanza.

American literature was releasing itself from its English parentage and was attaining a maturity and distinction of its own. In poetry Longfellow, Whittier, Emerson, Bryant, Poe and Whitman were recognized as worthy rivals of their English compeers and in prose Lowell, Hawthorne, Thoreau, Melville, Prescott and Oliver Wendell Holmes represented a galaxy which would make any nation proud.

In the previous year Helmholtz had invented the ophthalmoscope; Pravaz introduced the hypodermic syringe; Griesinger showed that ankylostoma was the cause of Egyptian anemia and Remak showed that growth of tissues was due to cell division. Two men, Darwin and Pasteur, were thinking thoughts that were destined to affect permanently the thinking and welfare of their fellow men.

In New York, on the day of incorporation of the Jews Hospital, the New York Times reported that the steamship "Great Western" was yet at anchor in the harbor; Jenny Lind was living in the City; a lot on 57th Street and Third Avenue sold for $475.00. The steamship "El Dorado" arrived from Chagres with 1,300,000 dollars in gold from California and an advertisement desired "a girl who understood the tassel business in all its branches." Among the amusements announced for that day, Lola Montez "will perform two grand ballets"; Don Pasquale was being performed in Niblo's Garden, tickets one dollar. Barnum's Museum was featuring a humorous farce "Caught in His Own Trap," followed by "Deaf as a Post" and a temperance play "The Bottle," admission was 25 cents.

* A more complete account will be found in a series of historical papers appearing in The Journal of The Mount Sinai Hospital, 1943–1944, and in The First Hundred Years of The Mount Sinai Hospital, Random House, 1952.

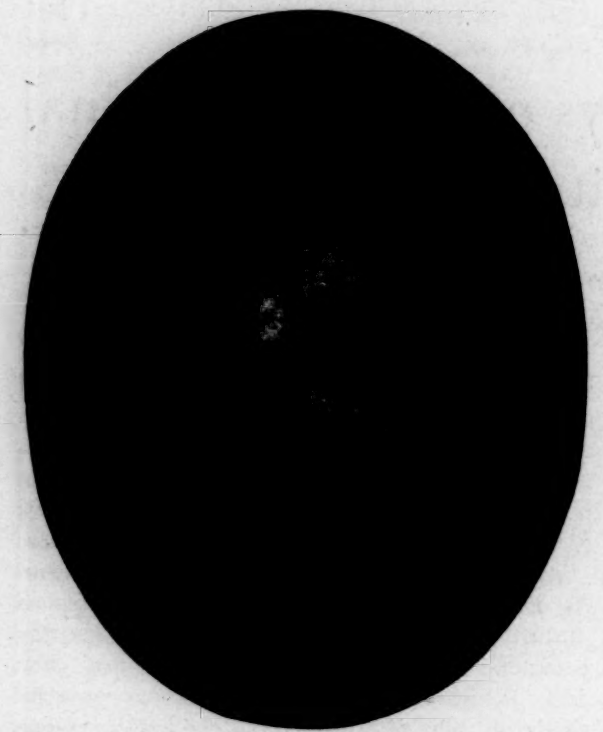

FIG. 1. Sampson Simson, distinguished lawyer and public-minded citizen of his day, who was the leading spirit in the founding of the Hospital and its first President.

A committee was organized for laying out a new park between 60th and 106th Street and between Fifth and Eighth Avenues to be known as Central Park. Dr. Rogers advertised his syrup of liverwort, tar and conchalogua in the following verse:

"The season of trial, cold winter, is here,
To the weak and the fragile a season of fear,
Cough, cold, influenza, bronchitis, catarrh,
On the lungs of the feeble have opened a war.
Oh! where in this peril shall these find a shield,
As ever consumption approach and life's citadel yield?
At the head of this verse stands the name of a cure,
Drawn from nature's dispensary, speedy and sure.
And to sum up its worth in a sentence, a breath,
To imbibe it is life, to neglect it is death."

In 1850 there were about 16,000 Jews in the City of New York which had a total population of 515,000. Their nucleus was twenty-seven Spanish and Portugese Jews who had fled to Brazil after their expulsion from their native land and who had become wards of the Netherlands which at that time governed Brazil. When the Portugese conquered Brazil, these Jews again sought a new haven and, in 1654, twenty-seven sailed from Bahia in the ship "Santa Catarina" for New Amsterdam. Upon arrival their possessions were sold by the master of the vessel at public auction in order to pay for their passage. Between the years 1820 and 1837 some German Jews trickled in and after the German Revolution of 1848 a considerable influx of well-to-do and cultured German Jews swelled the population so that by 1850 these constituted about half of the Jewish community.

From their first arrival in New Amsterdam the Jewish colonists had been enjoined by an Act of Toleration, as well as by their own ancient custom, to take care of their needy and sick. By 1850 this had become a formidable responsibility indeed because of the swelling tide of immigration and the ravages of cholera, typhoid, typhus and tuberculosis, which spread like wild-fire because of overcrowding and primitive sanitation. To provide more adequate facilities for their needy sick, a band of public spirited Jews led by Sampson Simson (Fig. 1), celebrated lawyer of the day trained by Aaron Burr, moved to the construction of the new hospital. For this purpose a plot of ground, 50 by 98 feet, was acquired on the south side of 28th Street between Seventh and Eighth Avenues. In 1852, 28th Street was in the rural outskirts of the City where goats wandered freely and where one could pick tomatoes, roast potatoes and build bonfires. The geographic center of the town was in the neighborhood of Barnum's Museum, situated on Broadway and Ann Street. There was only a scattering of houses above Washington Square.

On Thanksgiving Day, November 24, 1853, the cornerstone of the Hospital was laid. Franklin Pierce was then President of the United States. The Russians and Turks were battling in the East. Jenny Lind had given her farewell concert. The Sixth Avenue Railroad was completed up to 50th Street. Daniel Webster died on September 24th and on November 19th Thackeray gave his first lecture in the City on "The Four Georges." On the day before the cornerstone was laid Louis Napoleon was proclaimed Emperor of France and the second Empire was established. The New York Central and Michigan Central Railroad advertised "the shortest and most reliable train to Chicago." You took the steamer "Isaac Newton" at 6 P.M., arriving in Albany in the morning, then you

FIG. 2. The first Mount Sinai Hospital, 1855–1872, on West Twenty-eighth Street, New York City.

changed to an express train which reached Buffalo in thirteen and one-half hours; this connected with a boat that left Buffalo for Detroit at 8:30 P.M. and arrived sixteen hours later, connecting with an express train to Chicago. In the theatres, the Lady of Lyons, Money, The Rivals and Uncle Tom's Cabin were being given. The opera at Niblo's Garden was Le Prophete by Meyerbeer. The first Philharmonic concert of the season was on the 26th at the Metropolitan Hall. The Siamese Twins were on exhibition at the Broadway Menagerie and Museum.

In medicine the most noteworthy events were the publication of Marion Sims' treatise on the cure of vesicovaginal fistula, the discovery of neuroglia by Virchow and the establishment of the vegetable nature of bacteria by Cohn. Florence Nightingale was working in Scutari as the Lady of the Lamp and was on the threshold of her life work, the crusade to convert nursing into a cultural and dignified profession.

The new Hospital was made of brick, was four stories high and cost $30,000. The basement was occupied by a refectory, wash room and other utility rooms. The office was on the first floor and contained a marble tablet inscribed to the memory of Judah Touro who made a bequest of $20,000 toward its construction. A synagogue was on the second floor and the wards were on the remaining floors. The capacity of the Hospital was forty-five beds. A woodcut of the building (Fig. 2) shows an imposing front, four gracefully shaped windows to the floor.

On June 5, 1855, the Hospital was opened to receive patients. The first patient admitted was Louis Seldner; he suffered from a fistula-in-ano, which was cured by an operation by the attending surgeon, Israel Moses, an Army Surgeon. (Fig. 3.)

The New York Times of that day headlined a riot in Portland, Maine, because of an attempt

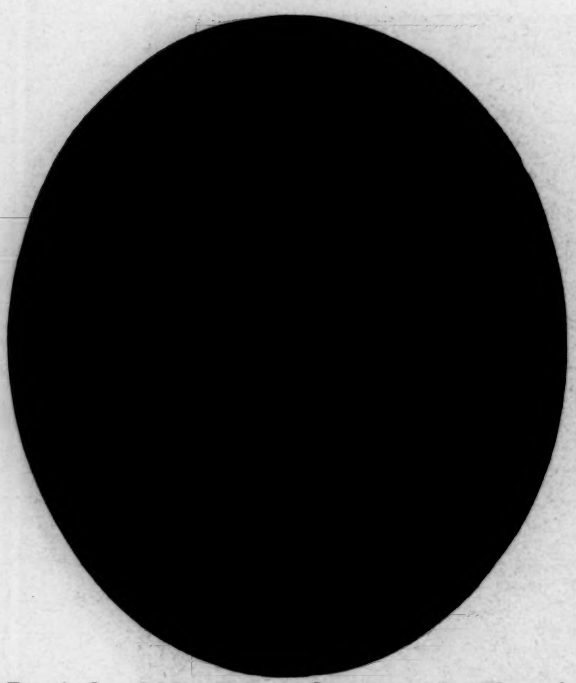

FIG. 3. Israel Moses, Army Surgeon who performed the first operation at the Hospital. He went on to a distinguished Army career in the Civil War.

by Neal Dow to enforce prohibition, and a Grand National Baby Show which was being held in Barnum's Museum. Buchanan was President of the United States and the notorious Fernando Wood was Mayor of the City of New York. Among other events that occurred in 1855 was the introduction of the Bessemer process for making steel, the opening of the College of Physicians and Surgeons on 23rd Street and Lexington Avenue, and also the founding by Marion Sims of the Women's Hospital in New York City. The project of uniting New York and Brooklyn was much discussed in some quarters.

The two years elapsing between the laying of the cornerstone and the formal opening of the Hospital were distinguished by a number of important medical discoveries. Von Graefe elucidated glaucoma and its treatment by iridectomy; Claude Bernard discovered the function of the vasodilator nerves; Graham investigated osmosis; Credé introduced his method of removing the placenta by external manipulation; Middledorpf introduced the galvanocautery; Manuel Garcia, a singing teacher, introduced the laryngoscope; Addison published his memoir on the suprarenal capsules; and Bunsen introduced his burner.

The professional staff of the Hospital from the outset included men of distinction in American medicine. One of the consulting surgeons of the original staff was Valentine Mott, a prolific operator. He is said to have amputated 1,000 thighs and his name is immortalized as the first to tie the innominate artery for aneurysm. He spent the last years of his life in travel, and it was during his stay in Greece that, full of the love of his profession and always ready for an operation, he tied the carotids of a cock in the valley of Epidaurus and sacrificed him to Aesculapius. The other consulting surgeon was Willard Parker who was the first in this country to open a perityphlitic abscess, in 1864. He was not aware that Hancock of London had done the same operation in 1848. It was said of Parker that "he could not be called a learned man but he was what some learned men never become, a wise one." The attending surgeons were A. B. Mott, son of Valentine Mott, Professor of Surgery at the College of Physicians and Surgeons, a founder of the Bellevue Medical College and of the first United States Army Hospital in New York; Thomas M. Markoe, a leader in surgery whose book on Diseases of the Bones was authoritative for many years; and W. van Roth of whom little is known. The consulting physicians were Chandler Gilman who held the chair of Obstetrics in the College of Physicians and Surgeons and in later years that of Medical Jurisprudence; W. B. McCready, a prominent consultant of his day; and William Detmold who founded the Orthopedic Clinic in the College of Physicians and Surgeons and was the first President of the New York County Medical Society in 1884. The attending and resident physician was Mark Blumenthal, who lived to the ripe age of ninety into the present century. I recall him at one of the earliest alumni dinners, a tall, straight, dignified man with snow-white hair and Burnside whiskers. His salary for the first year was $250.00. In subsequent years it was raised to $500.00. He was the first to perform an autopsy in the Hospital. The rule then was that the Directors must give permission. This was granted but by the narrow margin of one vote.

In the first full year of its existence, 1856, there were 216 admissions of which only sixteen were pay patients. There were fourteen deaths. At first only malignant, contagious or incurable diseases were rejected. These restrictions were

later modified and we find that patients with typhoid fever were accepted, provided "these be separated from the others and that their room be perfectly ventilated."

In the first annual report, of the year 1857, we find that there were altogether nine employees; one resident and attending physician, one house surgeon, one superintendent, three nurses, one cook and two domestics. The entire budget amounted to $1,684. The report also includes a number of case reports, for example, "A poor widow, in a wretched cellar of a tenement house, having three young children, was suddenly attacked with a violent fit of cramps. Having no means to pay a physician, and no friend to take care of her children, should she become an inmate of the Hospital, Dr. Blumenthal, with characteristic alacrity, attended her at her miserable abode, and she became convalescent. A few days afterward, she was attacked with typhus fever, followed by bilious fever and rheumatism. From these three horrid diseases she was cured. Still she remained feeble and debilitated, with no one to attend to her wants, and her misery was increased by the sight of her three neglected children. The Visiting Committee thought it best to remove her to the Hospital where she was perfectly restored to health."

There is a list of deaths in the 1861 annual report which is an eloquent reflection of morbidity in the middle of the last century. There were twenty-three deaths. Of these ten were caused by consumption, two from paralysis, two from pneumonia and one each from Bright's disease, marasmus, cancer of the liver, typhus, enterohelcosis,* cancer of the womb, meningitis, psoas abscess and suicide. The average age was thirty-five years. Patients did not live long enough to die from vascular disease, the public enemy number one today.

There were forty-six operations during that year, but this included nine catheterizations and the use of the actual cautery. The only operations that might be called major were a resection of the knee joint, a resection for cancer of the breast, and for a strangulated hernia; the last was the only laparotomy.

In the report of the year 1861 the name of Dr. Abraham Jacobi (Fig. 4) occurs for the first time. His close association with the Hospital

FIG. 4. Abraham Jacobi, long associated with The Mount Sinai Hospital and a notable figure in American medicine for many years. In 1878 he was made head of the first separate Pediatric Service for in-patient care of children to be established in New York City.

spans a period of fifty-nine years from 1860 to 1919, the year of his death; first as an attending physician, later as chief of the Pediatric Service, then as consulting physician and finally as President of the Medical Board, which he ruled with an iron hand from 1886 until the year before his death. He was small in stature but Olympian in personality. He possessed a broad culture, a fine sense of humor and an inexhaustible fund of memories which were tapped at the slightest provocation. He had the distinction of being the only consultant who had a double. He was in such demand that unscrupulous practitioners employed this double when they could not get the real thing!

Space does not permit me even to mention the developments of historical interest at the second site of the Hospital (Fig. 5), on Lexington Avenue between 66th and 67th Street—a change made necessary by such rapid expansion of activities as to outgrow the original edifice in

* Helcosis was an old term synonymous with ulcer.

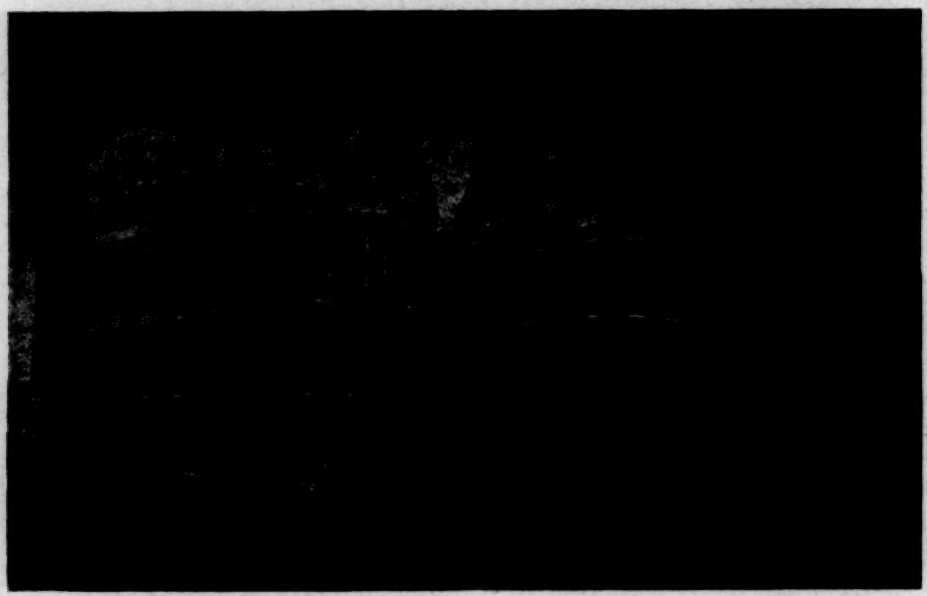

FIG. 5. Second site of The Mount Sinai Hospital, 1872–1904, on Lexington Avenue between 66th and 67th Street.

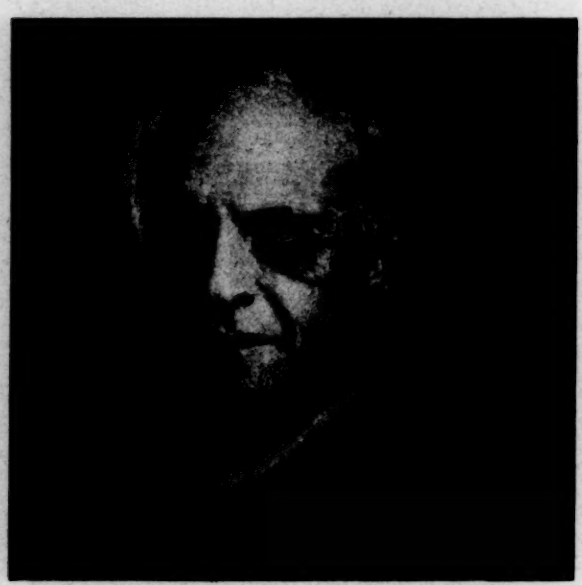

FIG. 6. S. S. Goldwater, pioneer in modern hospital design and planning, was for many years Director of The Mount Sinai Hospital. Later he served with distinction as Commissioner of Health and as Commissioner of Hospitals of the City of New York.

seventeen years. There was, for instance, the time when Mikulicz resected a heel, with Arpad Gerster as first assistant. As the instrumentarius at that operation I had a hard time keeping up with his lightning movements. Due to a tic his eyes were constantly blinking. I recall the day when Ludwig Aschoff conducted a clinical pathologic conference and another day when Robert Koch made rounds with Henry Koplik whom he embarrassed by asking whether he sterilized the butter as well as the milk against tubercle bacilli.

One could not write of The Mount Sinai Hospital, however, without commemorating five men who made a lasting impress upon its destiny and who, indeed, made their influence felt upon the course of American medicine: Arpad Gerster, whose surgical teaching is still a tradition; E. G. Janeway, a remarkably keen and quick observer; Emanuel Libman, who had rare clinical skill; S. S. Goldwater (Fig. 6), pioneer in modern hospital design and the first physician specialist in hospital planning; and George Blumenthal, President of the Hospital for twenty-seven of its more fruitful years, a forceful and decisive person, a man rich in ideas and in vision.

Of the last half of the centennial of The Mount Sinai Hospital, since 1904 at its third and present site, (Fig. 7) let the scientific contributions reprinted in the following pages of this memorial volume speak. They reveal the *genius loci* of the institution, the heritage of its far-seeing creators who viewed the Hospital as a living and growing thing, dedicated to the care of the sick, the study of disease and the teaching of the healing art.

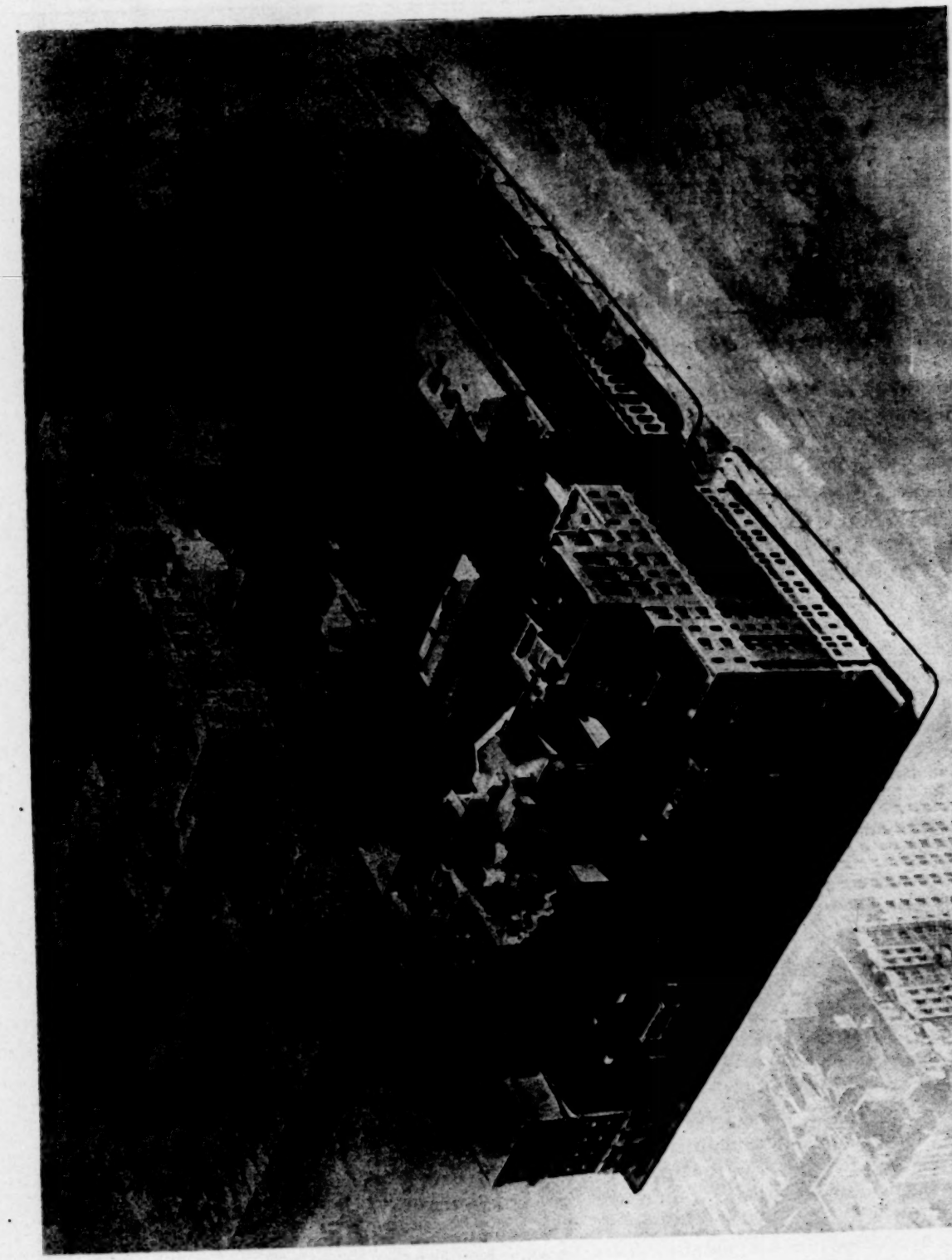

FIG. 7. The present Mount Sinai Hospital, housed in 22 buildings covering 7 acres, on Fifth Avenue between 98th and 101st Streets; total bed capacity 980, of which 557 are ward beds.

Reprints of Historical Interest

Thrombo-angiitis Obliterans: A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene*

LEO BUERGER, M.D.

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THERE is an interesting group of cases characterized by typical symptoms which the Germans have described under the name "Spontan-gangrän." In 1879 von Winiwarter published the results of the pathological findings in one case, and reported an obliteration of practically all of the arteries of the leg by reason of a chronic proliferative process, due, in his opinion, to a new growth of tissue from the intima. He, therefore, proposed a new name for this condition, namely, "endarteritis obliterans." Patients afflicted with this so-called endarteritis obliterans present symptoms which are so characteristic that the diagnosis is not difficult. I have had occasion to observe some thirty cases of this disease, and have made pathological studies on the vessels obtained from eleven amputated limbs.

The disease occurs frequently, although not exclusively, among the Polish and Russian Jews, and it is in the dispensaries and hospitals of New York City that we find a good opportunity for studying it in its two phases, namely, in the period which precedes and in that which follows the onset of the gangrene. We usually find it occurring in young adults between the ages of twenty and thirty-five or forty years, and it is because the gangrenous process may begin at an early age that the names presenile and juvenile gangrene have been employed. In one class of cases there are rather characteristic attacks of ischemia. The patients complain of indefinite pains in the foot, in the calf of the leg, or in the toes, and particularly of a sense of numbness or coldness whenever the weather is unfavorable. Upon examination we see that one or both feet are markedly blanched, almost cadaveric in appearance, cold to the touch, and that neither the dorsalis pedis nor the posterior tibial artery pulsates. When the foot becomes warm some color gradually returns. Some patients complain of rheumatic pains in the leg, others are able to walk but a short distance before the advent of paroxysmal shooting, cramp-like pains in the calf of the leg makes it imperative for them to stop short in their walk. Some of these cases give the typical symptoms of intermittent claudication. After months—or, in some cases—even years have elapsed trophic disturbances make their appearance. It is at this stage that another rather unique symptom makes its appearance: one which gives the foot the appearance typical of erythromelalgia. In the pendent position a bright red blush of the toes in the anterior part of the foot comes on rather rapidly, extending in some cases to the ankle or slightly above. Soon a blister, hemorrhagic bleb, or ulcer develops near the tip of one of the toes, usually on the big toe, frequently under the nail, and when this condition ensues the local pain becomes intense. Such trophic disturbances may at times make little progress and last for months; sometimes, however, the skin in the neighborhood shows cyanotic discoloration, and dry gangrene of the whole toe is an early issue. Even before the gangrene, at the ulcerative stage, amputation may become imperative because of the intensity of the pain. The left leg is usually

* Reprinted from *Am. J. M. Sc.*, 136: 567–580, 1908, with the kind permission of the publishers. To conserve space it has been necessary to omit the many striking photomicrographs which appear in the original article and also to abbreviate the text whenever this could be done without substantial loss.

This article segregated a clinical and pathologic entity out of a vaguely defined group of cases with peripheral vascular disease and correctly described its essential pathogenesis. Here designated obliterating thrombo-angiitis by Buerger, the disorder is generally referred to simply as Buerger's disease. A. B. G.

the first to become affected, although both limbs may show vascular disturbances almost simultaneously, and, when such is the case, the trophic changes, the ischemia or the reddening may give rise to a symptom-complex, often diagnosticated as Raynaud's disease. In short, after longer or shorter periods, characterized by pain, coldness of the feet, ischemia, intermittent claudication, and erythromelalgic symptoms, evidences of trophic disturbances appear which finally pass over into a condition of dry gangrene.

HISTORICAL. Although the literature bearing upon the pathology of the disease just described is large, I wish to call attention only to some of the more important contributions. Von Winiwarter and Friedländer ascribed the closure of the vessels to a proliferation of the cellular and fibrous elements in the intima, and therefore proposed to call the lesion by the name "endarteritis obliterans." This theory has been accepted by most authors, and even to-day, it is to be found in all the text books. Somewhat later, Wilonski pronounced the opinion that the essential change in the vessel walls was due to a multiplication of the elastic fibers, and proposed the name "arteritis elastica" for the condition. Perhaps the most important contributions are those of Weiss and Zoege von Manteuffel, because these authors placed an entirely new interpretation upon the pathological findings. Basing his paper upon the studies of his assistant Weiss, von Manteuffel suggests that the extensive occlusion of the vessels in this disease is dependent upon a primary arteriosclerosis; that the obliterative process commences in the popliteal artery, where it owes its inception to the formation of a parietal white thrombus; and that by virtue of a gradual extension of the parietal thrombus downward, followed by organization, a picture resembling an obliterative endarteritis is produced. In his cases the veins did not seem to be involved in the process. Von Manteuffel comes to the conclusion that the thrombosis is due to desquamation of endothelial cells, and that this occurs where the intima shows most advanced lesions of arteriosclerosis, namely, somewhere in the popliteal artery.

Two schools, then, have arisen among those who have made careful anatomical investigations: first, those who agree with von Winiwarter and who attribute the closure of the vessels to proliferation of the intima; and second, those who consider the process to be a peculiar type of arteriosclerosis in which desquamation of endothelium in the popliteal artery leads to the formation of parietal white thrombi and to occlusion of the arteries by direct peripheral extension from the primary focus.

During the last year and a half, through the kindness of Drs. Lilienthal, Gerster, and Sachs, of the Mt. Sinai Hospital, I have been able to make careful anatomical studies on eleven amputated lower extremities.[2] Although the results of the macroscopic and microscopic examination of the vessels agreed in part with the findings of other authors, a large number of additional facts were obtained which throw new light upon the pathology of the process.

GROSS PATHOLOGY. If we dissect out the vessels in these cases, we are struck by the fact that there is an extensive obliteration of the larger arteries and veins. Besides this, we find two other lesions which vary greatly in their intensity, namely, the periarteritis and the arteriosclerosis.

Upon making a large number of sections through such obliterated arteries and veins at different levels, we find certain characteristic appearances, which, in a general way, depend upon the age of the occluding process. Usually the vessel is seen to be filled with a grayish or yellowish mass that can be distinctly differentiated from the annular wall of the vessel, and that appears to be pierced at one point (more rarely at a number of points) by an extremely fine opening through which a minute drop of blood can be squeezed. Such obturating tissue is firm in consistency, and does not at all resemble the crescentic or semilunar occluding masses typical of arteriosclerosis. The vessel itself is usually contracted, so that its wall appears somewhat thickened. This picture is characteristic of arteries or veins which are the seat of a very old obliterative process, and is to be found most frequently in the peripheral portions of the vessels, although at times this type of lesion may extend throughout the whole length of the vessel, from the dorsalis hallucis almost into the popliteal.

As we trace certain of the obliterated arteries or veins upward, we are apt to meet with a change in the character of the obturating tissue. Frequently it becomes softer, more brownish in color, and terminates abruptly in the lumen of an apparently normal vessel; at other times the

[2] Since reading this paper eight additional cases have been studied.

brownish tissue gives way to soft reddish masses which are evidently the results of recent thrombosis. In some cases this thrombotic process occupies large portions of the vessel's course; in others, it is of short extent and terminates in a long cone of recent thrombus.

It is interesting to note that the veins share equally with the arteries in the lesion of occlusion. In some cases the veins are more extensively involved than the arteries, and this is particularly true of the collaterals of the posterior tibial, which are often closed when the anterior tibial veins are open. As for the arteries, we usually find an obliteration of a part or the whole of the anterior tibial, of the dorsalis pedis, and dorsalis hallucis, an occlusion of the posterior tibial and plantar vessels, with or without involvement of the peroneal. Sometimes the anterior tibial is practically normal in its upper half or upper two-thirds. More rarely a large portion of the dorsalis pedis is open, with the beginning of the occlusion in the upper part of this vessel or in the lower part of the anterior tibial. It is to be regretted that the termination of the process in the posterior vessels of the leg could not be determined in every instance because of the fact that amputation was done at a point where the posterior tibial was closed. In two cases, however, the popliteal and part of the posterior tibial vessels were found free; in others the popliteal could be felt to pulsate before the operation, and we can therefore conclude that in a number of cases at least the obturation does not attain the level of the popliteal artery.

Without giving a detailed description of the extent of the occlusion in all the cases, I may summarize by saying that we usually meet with obliteration of large territories with closure of the distal parts of the vessels, rather than the proximal; that there is often an involvement of some of the smaller branches, such as metatarsal and tarsal, but that the smallest arteries are free. The beginnings of the obliteration are not to be sought in the capillaries nor in the finest branches. If we follow the vessels upward, we frequently see a sudden cessation of the process, and in a number of instances we find that some 5 or 10 cm. of a vessel's length is closed and that the portions above and below are apparently normal.

The peculiar appearances presented by these terminations, the apparently normal condition of the vessel above and below the occluding masses, and the transition into thrombosed areas, all speak in favor of the view that we are dealing with a thromboarteritis or thrombophlebitis, rather than with a proliferative or obliterating process derived from the intima of the arteries and veins. The microscopic studies gave sufficient evidence of the correctness of this conception.

Besides the lesion of occlusion there are two other striking changes, namely a certain amount of arteriosclerotic thickening and periarteritis. The arteriosclerosis is never pronounced except in those rare instances in which the patient has suffered from the disease for many years and has reached the latter part of the fourth decade. As a rule, we note but a very slight degree of whitening or thickening of the intima here and there in the patent portions of the vessels. In a very few cases small atheromatous patches are present. There were deposits of lime in but one case, and these were of small extent.

A much more interesting and more important change is the fibrotic thickening of tissues immediately about the vessels, which I wish to discuss under the term "peri-arteritis." Wherever the vessels are occluded there is apt to be an agglutinative process which binds together the artery and its collateral veins, and sometimes also the accompanying nerve, so that liberation of the individual vessels by dissection is difficult. This adhesive condition is due to fibrous tissue growth, and varies considerably in its amount. At times we find little or no change about the occluded artery, at times fairly firm agglutination of the vessels in the sheath without much fibrosis, and at other times, so large an amount of connective tissue growth that isolation of the vessels or nerves becomes impossible, and the vascular structures make up one dense rigid cord. In a general way we may say that whenever both the collateral veins and the artery are occluded, we expect a fair amount of peri-arteritis, and that when but one vessel is affected, the perivascular change may be insignificant; and finally that the amount of peri-arteritis varies in the different cases as well as in the different territories affected by the disease.

Histology. The pictures presented by the vessels that are involved in this process are so varied, that I must confine myself to the description of those rather typical changes that have suggested the true nature of the process to me, and from a study of which we can see the development of the lesion from its incipiency to

its final maturation. I wish to point out: (1) The lesions of arteriosclerosis; (2) those that belong to the peri-arteritis; (3) the typical pictures found in the old obliterative process; (4) the differentiation of this lesion from the occlusive changes of arteriosclerosis; and (5) the various stages in the development of the occluding process from the beginning of the thrombosis to the final filling up of the vessel with dense fibrotic masses.

Both the arteries and the veins show varying degrees of thickening of the intima, the usual subendothelial changes with a fairly well marked hypertrophy of the internal elastic lamina without much proliferation of new elastic tissue in the thickenings of the intima. Of the two types of elastic tissue production pointed out by Jores, that which is dependent upon reduplication or hypertrophy of the internal elastic lamina is the more pronounced. Now and then in the older patients there are small plaques. Although the very small arteries may also be the site of thickening of the intima, this change is never sufficiently great to lead to complete or even marked obliteration of the lumen of the vessel. In the popliteal artery the formation of nodular thickenings is most extensive, but even here these are of moderate size.

The perivascular changes manifest themselves in a proliferation of connective tissue, in and around the adventitia, and are of two types, recent and old. Where the perivascular proliferation is active, the fixed connective tissue cells multiply and fibrous intercellular substance is deposited. Here and there small perivascular foci of lymphoid cells are found, but these do not seem to take an important part in the formation of connective tissue. In the old variety the fibrotic process appears to have come to a standstill, and the vessels and nerves are encased by dense bands of fibrous tissue, sometimes of a hyaline nature.

If we examine a cross-section of an artery or vein which is the seat of an old obliterative process, we often find an irregular, centrally placed lumen, a large amount of new-formed tissue occluding the original lumen, and certain changes in the media, the whole picture giving the impression that there is an extensive proliferation of the intima, namely an endarteritis obliterans (Fig. 1). From a consideration of the descriptions which are to follow, we will understand, however, that the new masses in the lumen are not derivatives of the intima, but owe their origin to organization of obliterating red thrombi. In the occluding tissue we find a fairly large number of capillaries, some blood pigment, and fibrous tissue which is either rich in cells (Fig. 2) or has already become sclerotic in nature. Where the process is oldest, there the capillaries are few, the connective tissue has become dense, the pigment has disappeared, and either in the middle or near the periphery of the obturating mass there is a large dilated vessel which is surrounded by connective tissue and which simulates the remnant of the original lumen. In other vessels there are large sinuses in the occluding mass (Fig. 3), or dilated vessels separated by dense connective tissue; or, there are atypical conformations in which two large blood spaces are separated by a septum that appears to spring from the intima of the vessel. The internal elastic lamina is thrown into marked folds, and between it and the connective tissue described, there may be a slight or moderate amount of fibrotic change in the intermediate layer of Eberth. The striking lesion of the media is the presence of capillaries with or without a small amount of lymphoid infiltration in their immediate vicinity (Fig. 4). Such capillaries may be present in small or in large numbers, depending upon the age of the process; where the occlusion is recent, the signs of activity in the media are striking, the capillaries plentiful, the cellular infiltration marked. The fine vessels come in from the adventitia, pass through the media, and penetrate the internal elastic lamina in order to vascularize the obturating mass.

What are the distinguishing features which enable us to differentiate an arteriosclerotic process from the lesions just described, and how can we establish the independence of the obturating masses from the intima from which most authors would have them arise? By the employment of the elastic tissue stains certain characteristics are brought to light which make it possible for us to say whether we are dealing with a thickening of the intima or with a new tissue lying in the lumen of the vessel. In arteriosclerosis we often find large obturating plaques which almost completely fill the vessel, the small space that is left being finally closed by a thrombus which becomes organized. It is not difficult to recognize such lesions as being arteriosclerotic when we note the large amount of elastic fibers in the plaque and note that these fibers are disposed for the most part parallel with

the internal elastic lamina (Fig. 5). In the occluding masses of so-called endarteritis obliterans, we find either a total absence of elastic fibers, or, when such are present, a growth of fibers around the larger canalizing vessels, particularly about those which are thick-walled and old (Figs. 6 and 7).

The most instructive histological pictures are those that are obtained in an examination of the vessels that are closed by transitional occluding tissue, and by this I mean obturation due to red thrombotic masses which can be traced into the softer brownish tissue and which finally may terminate in the dense old masses, the histology of which has already been discussed. In a number of cases and especially well marked in the vessels in an extremity which was amputated because of pain without gangrene, such transitions from areas of red thrombosis into the older stages were found. If we examine a vein or artery at or near the termination of the red thrombus, we find a fairly recent clot filling the lumen of the vessel without change in the vessel wall (Fig. 9). A short distance farther the clot becomes adherent in places and the corresponding portions of the media show beginning lymphoid infiltration and the earliest signs of vascularization (Fig. 10). At a point still farther removed, the aspect of the thrombosis has considerably changed. A number of miliary foci, not unlike miliary tubercles, make their appearance near the periphery, and there are evidences of organization such as the formation of capillary sprouts, fine capillaries, and fibroblasts (Fig. 11). The miliary foci present a central area of fibrin, and one or more giant cells (probably phagocytic in nature) with cells not unlike endothelial cells in a peripherial zone. Such giant-cell foci are but early stages in the process of organization. At another level the picture changes. The miliary foci gradually become lost, the vascularization of the clot becomes marked, the fibrin is almost absent, and numerous small round cells are scattered throughout. Here the media also shows quite a number of small capillaries with or without perivascular lymphoid infiltration. Whilst the fine vessels in the thrombus at this level are thin-walled, we soon note a change in their character. They become longitudinally disposed, here and there they connect with the media, they are surrounded by numerous round cells and fibroblasts and some blood pigment. These latter pictures correspond to the tissue which appears brownish and is not very firm. From this point on the transition into the old type is fairly rapid. The cells in the obturating mass disappear and the fibrous intercellular substance becomes abundant, some of the capillaries atrophy, others become dilated, forming large spaces with well defined walls; at times there are numerous sinuses giving a fenestrated appearance; at times there is a centrally placed vessel resembling a much diminished lumen of the origin vessel, and sometimes such canalizing vessels are centrally placed. With this final maturation of the organizing process there are certain concomitant regressive changes in the media, namely, a diminution in the number of capillaries and the disappearance of alien cellular elements.

We must not fail to interpret the nature of those pictures which would at first sight be mistaken for obliteration due to proliferation of the intima; namely, those in which there is a large canalizing vessel more or less centrally placed, surrounded by a fair amount of elastic fibers (Fig. 14). The paucity of elastic fibers in what would appear to be thickened intima, and the fact that the apparent remnant of the original lumen of the vessel usually divides at other levels into a number of smaller blood spaces, many of which finally communicate with the media, make it evident that we have here simply another product of the organizing thrombotic process.

Before closing the description of the vascular lesions it may be well to allude to some of the very interesting observations that were made in cases in which the thrombotic process was evidently of long duration. Here we frequently find that various stages in the organizing and thrombotic process may be represented not only in different vessels of the limb, but also in the separate members of a vascular sheath. Thus, the posterior tibial artery may be occluded by dense fibrotic canalized tissue through the greater part of its course, one of its accompanying veins showing an intermediate stage, another a very early process (Fig. 15). Still more striking are the appearances that were seen in the posterior tibial vessels of one case. Here the canalizing vessels had become very large and thick walled, and had become affected by the same thrombotic changes that had previously occurred in the parent vessel.

Pictures such as those just depicted not only point out the true nature of the process but are also suggestive of the historical development of

the lesion. They tend to show that there are frequent relapses or recurrences of the thrombosis, now in this, now in that vessel, at one time extending upward in a vessel already diseased, at another time affecting even the canalizing vessels themselves.

The Nerve Lesions. The study of the nerves in these cases is of considerable importance, both because the symptom of pain is such a constant and distressing one, and because some of the clinical features, such as the red blush of the foot in the pendent position, the transitory ischemia, and the cramp-like sensations in the calf, have all been in turn referred to some spinal or peripheral nerve disturbance.

In general we may say that the nerve lesions are secondary, apparently dependent upon the fibrotic perivascular changes. Thus we find considerable connective tissue proliferation around the nerve bundles, thickening of the perineurium, and even atrophy of nerve fibers wherever the peri-arteritis is marked and where the nerves are intimately connected with the vessels. In such places degeneration of many nerve fibers can be demonstrated by the Marchi method. The oldest perivascular connective tissue proliferation is then usually accompanied by the most intense fibrosis of the nerve sheaths. The popliteal nerve is usually free, as also the internal popliteal; whereas the anterior tibial and posterior tibial are more frequently affected.

General Considerations. We must needs regard the views of von Winiwarter and those who have agreed with him as fallacious, and have but to deal with the theory propounded by von Manteuffel. We would at first hand be led to the belief that the changes in the intima are in great part responsible for the thrombosis; for this is doubtless the case in the secondary closure by clot in cases of senile and diabetic gangrene. Zoege von Manteuffel takes the view that parietal white thrombi first lodged in the popliteal and gradually extend downward; that they remain mural in nature, are of the white variety, and are but rarely mixed with small red clots of recent origin. Practically every one of my cases furnished me with many evidences of the incorrectness of this conception. Thus, the large territories filled with red thrombi with their transitions into the old occluding masses, the frequent absence of any change in the upper parts of the anterior and posterior tibial arteries when very distal parts were occluded, and further, the presence of pulsation in the popliteal artery in some of the cases in which that vessel could not be examined, all speak against his assumption. We gain the impression that the obturation ascends rather than descends; for the firmest and oldest tissue is most frequently found in the distal parts and not infrequently terminates in young thrombi or soft rounded abrupt terminations in the middle or lower part of the leg. Finally, the presence of the same lesion in the veins, which Zoege von Manteuffel had evidently not encountered, could certainly not be explained in the light of his theory.

What then causes the extensive thrombosis of the veins and arteries? We are not able at this juncture to give a decisive answer on this perplexing point. Even to this day the determining causes of thrombosis are not completely understood, and it is therefore not surprising that here also we meet with difficulty. A number of factors must be taken into account, the arteriosclerotic change, the lesions of the media, the periarteritis, as pathological changes conducive to thrombosis; the external influences, as well as possible toxic conditions of the blood. We have already alluded to the fact that the changes in the intima do not appear to be responsible for the thrombosis. According to Lubarsch in his very recent summary of the literature on thrombosis, we must regard the changes in the intima as playing but a subsidiary role in this process; for, up to the present time it has not been clearly demonstrated that the endothelium contains any substance that can inhibit coagulation, nor has it been proved conclusively by animal experimentation that lesion of the intima alone suffices for the production of clot. Then again it is common occurrence to find extensive ulcerations and even calcareous plaques without the formation of thrombi. Even more significant is the fact that in arteriosclerosis the most extensive changes in the walls do not correspond to the site of thrombus formation.

In the vessels under consideration this independence of arteriosclerotic thickening and obliterating thrombosis is well illustrated, for in no place were we able to refer the origin of a clot to the presence of a thickened or diseased intima. Indeed, the popliteal artery which is apt to show the most marked arteriosclerotic change, is frequently free and patent. It becomes occluded only when the process has extended upward from its branches. Further, we fre-

quently find complete occlusion of the vessels whose walls are practically normal; and above and below such points the intima of the patent vessel may show a fair amount of arteriosclerosis. The white parietal thrombi which von Manteuffel claims to have seen adherent to arteriosclerotic patches, were never met with in the very great number of sections which we studied. On the other hand, it would appear that some of the thickening of the intima could be attributed to the process of organization of the thrombi, and we believe it to be, in a measure, secondary to that process. In a number of the cases cultures were made particularly from those portions of the vessels which showed the most active changes, and also from the hard sclerotic occluded portions, with negative results in every instance. It would seem therefore that at least the pathogenic bacteria are not present.

We must not forget the influence of static factors. Indeed the slowing of the circulation alone is a very important agent in the production of thrombosis, and it is rather significant that we so often encounter this disease in the lower extremities and that in all but one of our cases the disease began on the left side where venous stasis is more marked. Doubtless, then, a number of agents are at work in the production of the occlusion. Whatever may be the cause of the thrombosis, we feel inclined to take the view that, although the mechanical conditions that obtain in the lower extremities and the arteriosclerotic changes may be factors, some additional agent, be it toxic or otherwise, is at the same time responsible for the production of the periarteritis and thrombosis.

Viewing the process from the standpoint of the pathological lesions, and considering certain facts obtained by clinical observation, it would seem most plausible to assume that certain territories of either the arteries or the veins become rather suddenly thrombosed, in a fashion similar to the thrombotic process that occurs in the superficial veins of the lower extremities. Thus, at one time the dorsalis hallucis and dorsalis pedis, or perhaps plantar arteries or veins, could become closed by red clot; and then the process of organization would take place. Perhaps after an interval of weeks or months a similar process would cause extension upward, or affect other arteries and veins, until, after a lapse of many months, or a year or more, practically all the larger vessels would become occluded. It is from a study of the age of the process in the various territories that we are led to this supposition. Here too as in the superficial thromboses there is more tendency for the larger vessels to be involved than for the very fine ones; and although the process seems to ascend, it probably does not originate in the capillaries or smallest arterioles, but begins in branches of moderate size. The attendant peri-arteritis could be regarded as being either secondary, or possibly, as being produced by the same causes that lead to the thrombosis. Certain it is that the peri-arteritis is intimately linked with the presence of occluding masses.

Taking the true nature of the lesion into consideration, I would suggest that the names "*end-arteritis obliterans*" and "*arteriosclerotic gangrene*" be discarded in this connection, and that we adopt the terms "*obliterating thrombo-angiitis*" *of the lower extremities* when we wish to speak of the disease under discussion.

I wish to express my indebtedness to Dr. F. S. Mandlebaum, director of the pathological department of the Mt. Sinai Hospital, for the preparation of the photomicrographs which I have shown to elucidate certain points in my paper; I wish to thank Drs. Lilienthal, Gerster, and Sachs for giving me the opportunity of studying their cases, and to acknowledge with pleasure the valuable assistance rendered me by Miss Adèle Oppenheimer and Dr. Mark Cohn, volunteer assistants in the pathological laboratory of the Mt. Sinai Hospital.

An Acute Infectious Disease of Unknown Origin*

A Clinical Study Based on 221 Cases

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For many years great confusion prevailed about the two diseases which are now known as typhus and typhoid fever, even after clinical knowledge of these diseases had separated them from the large group of "pestilential fevers" with which they had previously been confounded. This confusion was due to the fact that, irrespective of the lack of pathological investigation and the ignorance of the causative factors of these diseases, no well systematized analysis of the clinical features of them had been carried on. At the end of the eighteenth and the beginning of the nineteenth centuries the first great work on the differentiation of typhus and typhoid fevers was begun. We owe to Prost,[1] in France, the recognition of the intestinal lesions as the important distinctive lesion of typhoid fever. Even with the great contribution of Petit and Serres,[2] who followed and elaborated on Prost's work, showing that the lesion was limited especially to the lower part of the small intestine, and of Bretonneau,[3] of Tours, that the lesion was always localized in the agminated and solitary glands of the ileum, the great acumen of Louis,[4] who gave the name typhoid, and of Chomel[5] could not dissociate clinically typhus from typhoid fever. They all regarded the contagious fever of camps, of armies, and that of the English writers as identical with the disease whose lesion they so meritoriously discovered and analyzed.

Just as important as this was the work at differentiation being done in Great Britain by James Muir,[6] Edmonstone,[7] Hewett,[8] of St. George's Hospital, Bright,[9] Alison,[10] Craigie,[11] Cheyne,[12] who were able to support the findings of the French authors, but only in a limited number of the immense number of cases at their disposal. Thus, it came about that the French pathologists rarely failed to find the intestinal lesions, for they were dealing with typhoid fever cases mainly, and the English investigators, who were dealing with much the greater number of typhus fever cases, rarely found the lesion. In 1835 Peebles[13] pointed out to Perry[14] of Glasgow, the *rubeoloid* eruption of typhus which he had learned to recognize in the typhus of Italy. Perry, thereupon, in the following year in a paper, correctly described many of the differences between typhus and typhoid, and showed the absence of the rubeoloid eruption in "dothienenteritis."

It was Lombard,[15] of Geneva, in 1836, who was the first to state definitely that there were in Great Britain two distinct and separate fevers, one of them identical with contagious typhus, the other a sporadic disease, identical with typhoid fever, or dothienenteritis, of the French. In Germany, however, as early as 1810, Hildenbrand[16] distinguished between the contagious typhus and the non-contagious *Nervenfieber*.

To this country belongs the honor of definitely

* Reprinted from *Am. J. M. Sc.*, 139: 484–502, 1910, with kind permission of the publishers. To conserve space this reprint omits several figures incorporating the temperature record of cases, the bibliographic references, and brief sections of the text.

This article is an example of acute clinical observation supported by simple bacteriologic and serologic tests, set down in precise detail and with great modesty. Events have proved that what is now universally known as Brill's disease is indeed an entity distinct from typhoid fever on the one hand and epidemic louse-borne and endemic murine flea-borne typhus fever on the other. It is, as Brill suspected it might be, "a peculiar typhus fever which has been evolved by modern improved hygiene and sanitation," or, in modern terms, a modified endemic form of typhus fever caused by Rickettsia prowazeki infection. A. B. G.

and firmly establishing the two diseases as distinct entities, owing to the epoch-making work and contributions of Gerhard and of Pennock,[17] of Philadelphia. They had studied in Paris under the great Louis, had been shown typhoid there, and on their return had investigated the disease in Philadelphia, but more especially an epidemic of typhus in Philadelphia in the spring and summer of 1836. They recognized the distinction between the disease of this epidemic and the typhoid fever in Paris demonstrated to them by the master clinician Louis. These observations were published by Gerhard in 1837, in February and August, and constitute the final differentiation between the two diseases. There is no chapter in the history of medicine more interesting and fascinating than the evolution of the clinical entities of typhus and typhoid fevers.

I have utilized this brief description of the course of the differentiation between these affections because it indicates how many workers in a field are necessary to establish the entity of any disease, the difficulty encountered, and finally the doubt which arises in many minds before final adjudication removes it. Bearing this in mind, I hesitate to submit the following theme which is based on an experience of 221 cases of an acute infectious disease which has probably for a long time, been considered by others as typhoid fever, but which I hope to show by definite clinical symptoms can have no relation to typhoid fever *per se*, but that it has a distinct clinical entity, entirely separate from typhoid, from typhus, or from any other disease known to me. My object in presenting this study is to enlist the attention of others who may have recognized the essential attributes of this disease, in the hope that by discussion the truth of my observations may be substantiated, or what would be equally advantageous to all, the error of my deductions be indicated.

There can be no doubt that the remarkable discovery of agglutinins by the work of Pfeiffer,[18] Durham,[19] Grünbaum, and that of Widal[20] in establishing the practical basis upon which serum reactions can be made in typhoid fever, has made the diagnosis of typhoid fever, by their demonstration in the blood, much more easy than before the discovery. Equally important with this reaction in simplifying the diagnosis was the establishment of the fact that typhoid fever is a bacteremia and is characterized by the presence of the Eberth bacillus in the blood, more or less constant, at all times of the disease. While no one symptom may be said to be characteristic of the disease, there are two signs whose presence establishes the disease peradventure. Fortunately these two signs are the most constant, in fact, the only constant factors of the disease: (1) The presence of agglutinins which occur in over 95 per cent. of all typhoid fever cases; (2) the typhoid bacteremia, or the presence of the Eberth bacillus in the blood of patients suffering with this disease, which is constant in over 90 per cent. of cases.

It would seem to me that a clinician would be stepping on very thin ice were he to make a diagnosis of typhoid fever in the absence of the roseola, of the enlarged spleen, of the Widal reaction, of the typhoid bacilli from the blood, from the stools, and the urine, of the symptoms of intestinal ulceration, especially if the fever of the infection ran but a ten to fourteen day course. He certainly would find it well nigh impossible to prove his position. If this proposition be true, its corollary may also be assumed to be true, viz., that given a disease of definite duration, twelve to fourteen days, having a most extensive non-roseolar eruption, giving no clinical signs of intestinal ulceration, with the Widal reaction invariably absent at all times of the disease, with no organisms in the blood at any time during its course, and with a fever that falls by crisis, such a disease is most likely not typhoid fever.

It may be noticed in this argument that I have made no reference to a pathological basis of the disease I am about to describe, or to that of morbid anatomy. I wish I could, because knowledge from those sources might establish the truth, as occurred with typhus and typhoid fevers in England and France just one century ago. But in my study of the disease which forms the subject of this communication, I have not met with a single fatal case and therefore can offer no contribution to its pathology and morbid anatomy.

History. The theme, as may be inferred from these preliminary remarks, is based on a careful clinical study of 221 patients suffering from an acute infectious disease, and was begun late in 1896 and carried on since then. At that time, with a fairly large typhoid fever service at Mount Sinai Hospital, I noticed a type of disease occurring mainly in the summer and fall months, somewhat similar, but characterized by many features irreconcilable to the picture of

typhoid fever, such as the course (being twelve to fourteen days), the temperature descent, which was mostly by crisis, the eruption, which was maculopapular and did not disappear on pressure, and the absence of the Widal reaction in this group.

Widal had just published the agglutination test which is now known by his name, and we began our investigations with it. What struck me forcibly was the positive results we got with the typhoid fever cases and the invariably negative results with this group which we had separated clinically from these cases. Our investigation was further carried on during 1897. We attempted to recover, if possible, either a typhoid bacillus or some other pathogenic organism from the feces, the urine, and, even at that date, from the blood of the spleen obtained by aspiration puncture, but with negative results. The results of this clinical work were published by me in an article entitled "A Study of Seventeen Cases of a Disease Clinically Resembling Typhoid Fever, but without the Widal Reaction, together with a short Review of the Present Status of the Serodiagnosis of Typhoid Fever."[21]

With the limited material of this type of disease at my disposal at that time, my judgment as to the eruption was not as matured as it is now. I spoke of the eruption being roseola and disappearing on pressure. This was a mistake which I have long corrected, and was occasioned by the fact that there may be found here and there among the spots of the characteristic type of eruption, a few which may disappear on pressure. Since that time I have constantly and persistently watched for similar cases, and have collected up to December 1, 1909, from my service and my colleague's at Mount Sinai Hospital, 221 patients with the following type of disease. The most of these I have seen personally.

DEFINITION. An acute infectious disease of unknown origin and unknown pathology, characterized by a short incubation period (four to five days), a period of continuous fever, accompanied by intense headache, apathy, and prostration, a profuse and extensive erythematous maculopapular eruption, all of about two weeks' duration, whereupon the fever abruptly ceases either by crisis within a few hours or by rapid lysis within three days, when all symptoms disappear.

[21] N. E. Brill, New York Medical Journal, January 8, 1898, and January 15, 1898.

GENERAL DESCRIPTION. After a period of three or four days, during which the patient suffers from malaise, loss of appetite, nausea, and slight headache, the disease begins rather abruptly, many times with a chill or chilly sensation. This is followed occasionally by vomiting, by general body pains or pain in the back; epistaxis sometimes occurs. The headache now becomes intense and apathy and prostration supervene with the rapidly rising temperature. The fever reaches its height in two to three days, when it remains constant thereafter, the temperature showing but slight diurnal remissions. During the fastigium of the fever the patient lies very quietly, sometimes moaning or groaning, with facial expressions of pain shown by the contracted and furrowed brow. His eyes are dull and suffused, his conjunctivæ congested, and his face, especially over the malar prominences, flushed. He is rather drowsy, his sensorium dulled, and he resents being disturbed by more marked expressions of pain; any attempt to move him increases his headache. The tongue is usually coated and moist, only occasionally is it dry and furred. The skin of the body feels hot and dry. The headache remains intense without diminishing in severity, and about the sixth day a rash appears. The eruption is found over the abdomen and back, and quickly spreads to the thorax and to the arms and thighs and occasionally to the neck, forearms, hands, legs, and feet. I have seen the whole body, even including the palms and soles, excepting the face, covered by the eruption. The rash is dull red in color, very slightly raised, and when subjected to pressure does not disappear. The individual spots on pressure fade slightly in color, and only very rarely can they be obliterated, but return to their florid efflorescence as soon as pressure is removed. The bowels are obstinately constipated, as a rule, and in many cases can only be moved by laxative agents. The pulse is full, rather slow, not nearly as rapid as might be expected with the pyrexia. It is soft and of low tension and often dicrotic. These symptoms remain in full development until about the twelfth day, when the fever abruptly disappears, the patient's temperature suddenly dropping in a few hours to normal, the rash fades, the headache leaves, the apathy and prostration vanish, and the patient feels perfectly well, taking an interest in his surroundings. A rapid convalescence follows. During the progress of the disease slight emaciation may develop, but rarely very marked. The

urine is scanty, high colored, and at times contains albumin. Delirium is only exceptionally noticed, and then only at night in the patients with hyperpyrexia. A few patients show rigidity of the neck, and the presence in them of the Kernig sign may be elicited.

ETIOLOGY AND ANALYSIS OF SYMPTOMS. I have selected the histories of the last 50 cases of my series, chiefly because these histories were readily accessible and because I have had the symptoms tabulated for the purpose of comparative study. These 50 cases have come under my observation since June, 1906, and extend to December 1, 1909.

Sex. Males show a greater tendency to be affected than females. There were 34 males and 16 females.

Nativity. Inasmuch as the largest number of patients at Mount Sinai Hospital are Russians. Russia leads the list of cases with 30; Austria, 12; United States, 2; Ireland, 2; Germany, 1; not noted, 1.

Month. By far the largest number of cases occur in the summer months. Of this group there were 1 in January, 3 in February, 3 in March, none in April, 3 in May, 8 in June, 8 in July, 2 in August, 6 in September, 11 in October, 3 in November, and 2 in December.

Age. The disease is most common between the twentieth and fortieth years of life. In this group 33 appeared in that period: First to second decade, 9 cases; second to third decade, 19 cases; third to fourth decade, 14 cases; fourth to fifth decade, 4 cases; fifth to sixth decade, 2 cases; sixth to seventh decade, 2 cases. The youngest patient of this group was aged seventeen years, the oldest was sixty-five years.

Contagion. I can find no evidence of the disease being directly communicable. In the 221 cases we have not had, so far as I can learn, two members[22] of the same family, nor two from the same household or same house. The patients are admitted into the general wards, and the disease has never been communicated to any other occupant of that ward; nor has the disease ever arisen among the patients in the hospital.

Food Poisoning. It might be asked whether the disease has any relation to the ingestion of certain foods or to the toxins contained in decomposing food. The *prima facie* evidence seems to be against this view, for, if such were the cause, the disease would necessarily be widespread in special districts and affect many in a single family.

Incubation. The period, before the acute symptoms begin, varies in duration from sudden onset without premonitory symptoms to fourteen days. In 15 of this group of 50 cases the incubation period could not be ascertained, in 35 it varied from a few hours to fourteen days. The average of this stage of the disease was four and eight-tenths days. During it the patient suffered with malaise, fatigue, anorexia, constipation, dull feeling in the head or a distinct headache. Sometimes he complains of nausea and indigestion and painful sensations over the body. After this stage the disease in its intensity may be said to begin.

Onset. This may be sudden, when it is marked by a distinct chill, or chilly sensation, with increased general body pains or pains in the back, by nausea, and sometimes by vomiting. Now the headache becomes intense. Or the onset may be gradual, when it cannot be separated from the incubation period. In the latter case only the development of the fever and the increasing headache permit one to define this stage of the disease. In 19 cases the onset was sudden; in 31 the disease began gradually.

Epistaxis, while it occasionally occurs, is not common. It was noted during the course of the disease in three cases.

Headache. This is one of the most pronounced features of the disease and is almost invariably present. It may start in with the incubation or it may not appear until the onset. It becomes intense and at times agonizing, and in severity is only equalled by the headache of a meningitis, of a cerebral tumor, or the head pains occasionally present with syphilis. It lasts, as a rule, in all of its intensity throughout the disease, and then only disappears with the crisis. In the latter respect it differs from the headache of typhoid fever, which, as is well known, diminishes in intensity in the second week of that disease and is then no longer the chief subject of the patient's complaints. In this disease the headache is much more severe, and it lasts throughout its course until convalescence begins. The headache is general and is not confined to any locality of the head, being as severe in the occiput as in the frontal and temporal regions. In the cases in which the headache is most intense rigidity of the neck is sometimes observed; when the latter

[22] Since this was written I have had the opportunity to see at Bellevue Hospital, through the courtesy of Dr. Warren Coleman, four members of one family who were attacked almost simultaneously with this disease.

is present, a distinct bilateral Kernig sign may be observed. Rigidity of the neck and Kernig's sign were noted in four patients of this group. Lumbar puncture was made in these four patients, and the cerebrospinal fluid was examined culturally and cytologically. The growth was sterile in all, and the proportion of lymphocytes was slightly increased. The headache was agonizing in 8, intense in 33, and moderate in 9. With rigidity of the neck, there may be contracted pupils and, rarely, muscular twitchings and active reflexes.

Facies. The patients suffering with this disease look sick, much more so than a patient in the corresponding period of typhoid fever. The face is flushed, especially deeply over the malar prominences, the flush being, sometimes, not noted about the nose and mouth, which then may look unusually pale. The conjunctivæ are congested, the eyes suffused and later may become dull in expression. The forehead is wrinkled and the brows drawn together giving the expression of headache with which they suffer. The attitude in bed is generally relaxed, the patient being inordinately quiet. He does not toss about, as motion increases the headache. He resents being disturbed, and responds with reluctance to questions. He utters moans and groans and points to his head when asked where he suffers. It would seem to me that the physical relaxation and the indifference shown to the examiner represent an apathy which is only disturbed by an attempt to move him. This apathy is marked in most of the cases. In 6 of our group it was extreme, it was marked in 17, and absent in 12. In 15 the condition was not recorded.

Prostration. There can be no doubt, after one has seen a few of these patients, that this symptom is a striking one. It is marked by the general muscular relaxation, the posture of the patient in the bed, the indifference of the patient to his surroundings, and his lessened ability to move. It usually corresponds in intensity with the intensity of the infection, and is more marked with patients showing a hyperpyrexia than in the milder cases of the disease.

Skin. During the course of the disease the skin is hot and dry. Between the fifth and seventh day of the disease a maculopapular eruption appears, first on the back and abdomen and then over the trunk. The rash may spread rapidly, and in a great number of cases the arms and thighs may be covered. In a few cases the eruption involves, in addition, the neck, forearms, hands, legs, and feet, even exceptionally the palms and soles. At times the eruption is more profuse on the extremities than on the trunk. The eruption does not appear in crops, as in typhoid, but the spots appear synchronously over the area of the body which they invade. Each spot lasts throughout the rest of the course of the disease. It is noticeable that the rash is the most profuse when the attack is most severe. The spots are distinctly maculopapular, are only slightly raised and may be designated as an erythema. They are dull red in color. They vary in size from two to four millimeters, are uneven in contour, and are irregularly round or oval, their periphery being commonly diffuse and indistinct. If subjected to pressure they do not disappear, but fade slightly. This is best tested by pressing them with and under a glass microscopic slide, when all gradations of pressure effects may be observed. The eruption is more nearly morbiliform or rubeoloid than roseolar. In three of this group the eruption in places was distinctly petechial, suggesting a typhus fever eruption more than any other eruption.

From this description it may be seen that the eruption in no respect resembles that of typhoid fever, the eruption of which is characteristically papular, circumscribed and lenticular, appears in crops, very rarely involves the extremities, is never more profuse on the extremities than on the trunk, has never to my knowledge been observed to attack the palms and soles, and almost always disappears completely on pressure excepting in "hemorrhagic typhoid fever." The eruption of typhoid fever consists of hyperemic spots; in this disease it is distinctly erythematous, some of the capillary contents escaping into the surrounding tissues, leaving a more or less permanent zone which pressure cannot remove. I have looked for the subcuticular mottling of typhus, but have never observed it in these cases.

The eruption does not begin to fade until the crisis, then it rapidly becomes paler, and in two days thereafter only dirty yellowish-brown stains mark the site of the former spots. When petechiæ are present, the punctate hemorrhages disappear much more slowly. The rash is not nearly as discrete as it is in typhoid, for two or more spots frequently coalesce, a condition which is commonly seen. I have never observed the eruption on the face, but have seen it occasionally extend up the sides of the neck, involving

the skin over the mastoids and even the back of the ear. Contrary to the typhoid eruption, which, as a rule, is not abundant, but occurs in varying crops of ten to twenty in number, this is, as a rule, an abundant eruption. In our series the following was the distribution of the eruption: Abdomen, chest, and back, 13 cases; abdomen, chest, back, arms, and thighs, 22 cases; abdomen, chest, back, arms, thighs, forearms, and legs, 9 cases. Distribution not noted, 6 cases. Of those with profuse rash involving the forearms and legs—9 in number—the eruption was observed on the palms and soles in 4, and on the neck in 3 cases.

Herpes. Labial herpes was noted as an accompaniment in 3 out of the 50 cases.

Pulse. The pulse rate, considering the fever, is not very high; it averages between 86 and 100 beats per minute. It is full, soft, and of low tension. Dicrotism is not infrequently observed.

Temperature. The course of the fever is rather distinctive. The patients' temperature begins to rise at the onset, usually three or four days after the stage of incubation, and then with rapid strides, so that on the second or third day from the onset it may have reached its fastigium. It then averages between 103.6° and 104.2°. It is but slightly higher in the evenings, and continues high throughout the rest of the disease. The remissions between morning and evening seldom exceed 1° F. With the exception of these remissions the temperature remains constantly and uniformly high until the day before the critical fall, when a precritical rise may occur. In four of these 50 cases a precritical rise between 105° and 106° F. was observed. The precritical rise, however, is not the rule and only occasionally occurs. On the twelfth to the fourteenth day the temperature begins to drop. The fall is quick and abrupt, and in some of our cases within ten hours from 105° F. to normal. The critical fall occurs in a large number of the cases. In also a fair proportion of the group the temperature falls by rapid lysis (Figs. 1, 2, and 3). In this connection we have assumed as a standard by which judgment may be expressed the following: A crisis to be a fall in temperature to normal within twenty-four hours; rapid lysis to be a fall to normal in forty-eight hours; and lysis to be a fall to the normal within seventy-two hours. As a rule, after the fall, whether by crisis, rapid lysis, or lysis, the temperature does not rise again. Exceptionally a short rise, lasting but a few hours or a day thereafter, was observed. The most remarkable feature of this disease is that with the fall in fever all the signs clear up, and the patient, who may have felt and looked very sick, becomes alert, interested in his surroundings, and says he is well; the headache is dispelled, as if by magic; the eruption rapidly fades, and convalescence is established. In this group there was a critical fall in 16 cases, a fall by rapid lysis (less than forty-eight hours) in 17 cases, a fall by lysis in 17 cases. I have not seen a single patient whose temperature took more than sixty hours to fall to the normal, excepting with a complication.

Constipation is a marked feature of the disease. It was present in 42; in 6 the bowels were regular, and in 2 there was a diarrhœa following a previous constipation. Very frequently the bowels can only be moved by the use of cathartics. Blood has never been found in the fecal discharges, either macroscopic or microscopic. The guaiac and benzidin tests for occult bleeding have been negative.

Tympanites is not a feature of this affection. In 9 cases a slight abdominal distention was observed.

Spleen. This organ is frequently enlarged to palpation. In 27 cases of the series it was distinctly palpable below the costal margin. At times the spleen extends for a considerable distance below the ribs, four centimeters below being the maximum. In 16 cases it was one centimeter below; in 7 cases, two centimeters; in 2 cases, three centimeters; and in 2 cases, four centimeters.

Mental Symptoms. The apathy and dulled sensorium have been mentioned in the general description. Delirium is only occasionally present, and it does not assume the active type so commonly seen in typhoid fever. It usually occurs in those running a high febrile course, and then only at night. It is muttering in character.

Blood. The average white blood cell count is higher than it is in typhoid fever; there is not the tendency to leukopenia which typhoid fever blood shows, the count being between 9000 and 11,000. When bronchopneumonia exists as a complication the count is, of course, higher; our highest in such a case was 23,600. The average of the series—in only one case was no white blood count noted—was 9394, the lowest being 4200 and the highest 23,600, the last being in the patient with bronchopneumonia. The

average count of polymorphonuclears was 69.4, and the lymphocytes, 30.6 per cent.

Urine. The urine is generally high colored and clear. It contains a faint trace of albumin in many cases and occasionally granular casts. Albumin was noted in 19 of the cases. The diazo reaction is not infrequently obtained, but it is more frequently absent than present. It was demonstrable in 9 cases, and no reaction could be elicited in 30; in 11 cases it was not noted.

Agglutination Reactions. In the 221 cases there has not been a single positive reaction to the Widal test. The test has been carried on perhaps much more assiduously than would have been the case had positive results been obtained. The blood has been sent to the laboratory daily in most all of the cases, not only during the course of the disease, but during the period of convalescence until the patient left the hospital. No positive reactions have been obtained. Tests were made in dilutions of from 1 to 20, and in some cases up to 1 to 1000, because it has been shown that agglutinations with the typhoid bacillus in some cases of typhoid fever are demonstrated only in high dilutions. Agglutination tests were also made in some of the cases with various paratyphoid bacilli, with several colon strains, and in a few cases with the Gärtner bacillus. The results were all negative. I believe that the absence of positive results speaks very strongly against these cases being due to infection by the typhoid bacillus or members of the intermediate group.

Bacteriology. The evidence of infection by the recovery of the offending organism in this disease is entirely wanting. Since 1896 we have persistently tried to isolate a specific organism from these cases, but without success. Blood cultures have been made in a very large number of the cases. During the past three years cultures have been made from all of the cases that have come under observation. The cultures in these cases were made under the direction of Dr. Libman. The methods used in this work during the past three years are the same as those that were used in the studies of the bacteremia in typhoid fever made by Dr. Epstein.[28] Dr. Epstein obtained positive results in nearly all of the cases of typhoid fever. This makes all the stronger the proof that in the set of cases which I am describing we are not dealing with typhoid fever or paratyphoid fever.

The clinical aspect of the disease is strongly in favor of its infectious nature because it has a definite incubatory stage, one of onset, one of duration, and one of decline. We regard typhus fever, measles, scarlet fever, and the like as infections, and have no definite knowledge as to the nature of the infection, hence the absence of such knowledge as to this disease should not militate against considering it an infectious disease.

Previous Typhoid. We carried on an inquiry based on immunity which typhoid fever gives to the one who suffered previously from typhoid, and found that in the group of 50 there were 10 who had had typhoid fever previously, 37 who had not suffered from typhoid fever, and 3 could give no information concerning previous illnesses.

Relapses. I have never seen a relapse in this disease. When the temperature once falls the disease ends. Unless there be a complication the fever does not rise again. This is so entirely different from the course of typhoid infections that in itself it would cast a serious doubt on the probability of this disease belonging to the typhoid fever group, with which some of my professional colleagues insist it belongs.

Complications. *Bronchitis* is a common accompaniment of the disease and is present to a greater or less degree in the majority of the patients. When it develops, it is seen early, sixth or seventh day. It lasts as a rule, throughout and disappears in convalescence.

Bronchopneumonia was observed in 3 of the group.

Meningismus. What clinicians call signs of "serous meningitis," such as rigidity of the neck, contracted pupils, the presence of bilateral Kernig phenomenon, stupor, etc., are sometimes present. These signs were noted in four of the 50 of this group.

Phlebitis cruris was observed once. *Otitis media* occurred in one patient. *Cystitis* was observed twice, but I think it was due to some error in the technique of catheterization, which was done on both these patients.

Duration. The disease lasts about two weeks. In our series the average duration was thirteen and three-tenth days. In one case it lasted five days and in one, twenty-two days. The last case, however, was accompanied by a bronchopneumonia and it was difficult to determine when the original infection terminated. The detail of the series is as follows:

5 days . . .	1 case	14 days . . .	5 cases
6 days . . .		15 days . . .	5 cases
7 days . . .	1 case	16 days . . .	2 cases
8 days . . .	1 case	17 days . . .	3 cases
9 days . . .	1 case	18 days . . .	
10 days . . .	2 cases	19 days . . .	1 case
11 days . . .	4 cases	20 days . . .	
12 days . . .	13 cases	21 days . . .	
13 days . . .	10 cases	22 days . . .	1 case

It will be seen from this that almost half the cases terminated between the twelfth and thirteenth days. This has been our experience with the rest of the 221 cases. A prediction may almost be made that the disease will terminate on one of the two days just stated.

Typhoid.	*Unknown Infection.*
Usually long incubation.	Short incubation, four to five days.
Onset not commonly abrupt.	Commonly with chill or chilly sensation.
Fever; gradually increasing ascent of temperature to fastigium—in all about ten days.	Fastigium reached in three days.
Remissions of temperature occasionally more than a degree.	Rarely more than one degree.
Fall usually by gradations to normal, taking commonly one week.	Fall commonly by *crisis*, not longer than sixty hours.
Eruption, circumscribed, lenticular, papular.	Maculopapular, periphery indistinct and irregular.
Distribution, chiefly, back, and abdomen, seldom appearing on upper and lower extremities; almost unknown on palms and soles.	Distribution in addition to trunk on upper and lower extremities not infrequent, on palms and soles occasionally.
Eruption appears in crops throughout the disease.	Does not appear in crops.
Spots rarely confluent, and then confluence of but two spots.	Confluence may occur with three or four spots forming a number of patches.
Roseola disappearing on pressure.	Erythema, not disappearing on pressure.
Petechial spots (hemorrhagic) very rare.	Petechiæ occasionally.
Apathy and prostration late in development.	Apathy and prostration early.
Labial herpes rare.	Labial herpes in 6 per cent. of the group.
Diarrhœa fairly common.	Constipation an almost invariable accompaniment.
Hemorrhages from the bowel often observed.	No intestinal hemorrhages or blood in feces.
Headache disappears in second week.	Is more intense and lasts throughout the disease.
Relapses observed by all observers.	Relapses have never occurred.
Widal reaction positive in over 95 per cent. of the cases.	Widal reaction invariably absent.
Blood cultures positive in over 90 per cent. of the cases.	Blood cultures invariably negative.
Convalescence slow.	Convalescence speedy.

DIFFERENTIAL DIAGNOSIS. Inasmuch as these cases have been considered by almost all my colleagues in New York, in the past, as typhoid fever cases, it will be necessary to show the marks of differentiation. The (preceding) parallel column offers itself for this purpose as most convincing.

Typhus Fever. In the case of an epidemic of typhus fever, in my opinion, it would be simply impossible to say that these cases which I have described were not mild typhus fever. From the clinical aspects no lines of demarcation can be fixed. The onset, the eruption, though subcuticular mottling is absent, the critical decline, the absence of relapses are almost identical in both. If one can believe that typhus fever has been so modified by modern conditions of hygiene as no longer to be communicable, but to exist at all times in a community, to have lost its notoriously epidemic character, and to have been deprived of the grave nervous symptoms and its toxemia so as to be a non-fatal disease, then one could say that these cases deal with a modern typhus fever, or rather with a peculiar typhus fever which has been evolved by modern improved hygiene and sanitation. The preference of the disease for developing in the summer months is against the probability of its being typhus. Clinically this disease resembles typhus fever more than it does any other disease, and I should have felt that I had offered nothing to our nosology if it had been proved that typhus fever had lost its virulence, that it was constantly present in a community, that it was not communicable, that when it was present epidemics of it did not occur, and that it was no longer a grave and fatal disease. But with typhus fever, as the great masters of medicine have taught, and as I have seen it, such a conception would be unjustifiable; therefore, I believe this disease not to be typhus fever.

Meningitis. The occasional occurrence of signs of "meningismus" in this disease might suggest epidemic cerebrospinal fever ("spotted fever"). There would be no very great difficulty in determining the presence of that disease if spinal puncture were carried out and the cerebrospinal fluid examined culturally. Its cytology and bacteriology are definite, and the recovery of Meningococcus intracellularis would settle the diagnosis.

Influenza. In epidemics of this disease some cases might appear which have a great similarity to our disease. Those of us who dealt with the

type of influenza as it appeared here in 1890 will no doubt recall cases very similar. The protean forms that were then observed would very likely suggest that perhaps this disease might be one of the multivaried or protean forms of influenza. Influenza appears pandemically, is very sudden in its onset, and prostration is the earliest symptom; it has no definite incubatory stage; it is accompanied by signs of cardiac weakness with rapid pulse and often with diarrhœa. It is par excellence the disease of complications and sequels, and especially of slow convalescence.

Prognosis. Thus far it has been invariably good. No fatalities have ever occurred in my cases. Sick as the patients are and grave as the symptoms sometimes appear to be, one ought from this experience be justified in predicting a favorable issue to the disease.

Treatment. This for the present should be entirely symptomatic. Personally I have used no stereotyped plan. The usual remedies have been employed for the symptoms which required relief. The diet has been restricted to fluid and soft nourishment. For the present I deem it wise, especially in cases occurring in institutions to use the usual precautionary measures which are employed in typhoid fever cases to prevent infection; nurses are so instructed in handling these patients. Such precautions, however, would seem to be unnecessary; nevertheless in the indefinite state of knowledge concerning the causative factors of this disease no injury can be done in using preventive measures.

Epicritical. More difficult than separating this group from typhoid fever, among which it has been in all these years included, is the difficulty of giving a name to this disease. To my mind there can be no doubt that the clinical picture is so definite, so marked that it cannot escape recognition. If this should be the view of others, the disease must represent a distinct clinical entity. I am convinced it does and is entitled to a place in medical nosology. There is no sign in the clinical picture which would characterize the disease. The critical fall is definite and I thought it might be wise to use that feature for a provisional name, calling the disease "critical fever;" but pneumonia and typhus fever are likewise critical fevers. On this account the name is not desirable. I should emphatically deprecate calling the disease "pseudo-typhoid fever" because the affection has nothing in common with typhoid, paratyphoid, and typhoid-colon, or intermediate group infections. Some years ago, before we had done reliable blood work on this group, I believed that it might represent paratyphoid infections, and so I wrote,[27] but retracted that idea long ago, after I had convinced myself that the disease had nothing in common with paratyphoid. If it be typhus fever Health Boards should take cognizance of the fact that there exists in New York City at all periods of the year a non-fatal and non-contagious typhus fever which may possibly give rise at any time to an epidemic, though it has not done so in the last fourteen years. For the present, owing to ignorance of the pathology and etiology of the disease, I deem it wise not to give a name to the affection. I prefer to speak of it as an "acute infectious disease of unknown origin." My chief desire, in recalling to the attention of the profession this disease group, is to enlist its attention, in the hope that other observers may find similar or identical cases. Let us trust, if they do, that they can give us more definite and accurate knowledge than I have been able to offer. If this be the result of this contribution, or, if further inquiry shows that my attempt to establish a clinical entity has been based on poor observation and defective deductions, I should have almost as great satisfaction as would corroboration and additional proof bring to me, for it would have further and more forcibly taught me that while it is human to err, still truth will always prevail.

Removal of Neoplasms of the Urinary Bladder

*A New Method, Employing High-frequency (Oudin) Currents through a Catheterizing Cystoscope**

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New York

THIS brief preliminary report is written with the object of calling the attention of the profession to a new and simple method of destroying new growths of the urinary bladder. Even though my experience is not extensive, limited as it is to two large papillary growths, still the observations made leave no doubt in my mind that the Oudin current, employed as I have employed it, will prove effective in the cure of benign papillomata, as well as useful in malign tumors, papillomatous or not, both as a hemostatic and as a cauterizing agent. My experiences also suggest the usefulness of these currents in many other conditions both in the bladder and in other parts, e. g. tuberculous ulcers of the bladder, prostatic hypertrophy, growths in the urethra, etc.

In March, 1908, I hit on the idea of using the high-frequency current as I now use it. Expert electric manufacturers told me I could not obtain the effects I desired through a water medium; that an air gap was necessary. Moreover, that if I used the current as I intended, it would burn out my cystoscope. Others who had experience with these currents in skin conditions were equally pessimistic. Despite these opinions I ordered from the manufacturer a thoroughly insulated cable, No. 6 French caliber, so that it could be introduced readily through the catheter tunnel of a Nitze catheterizing cystoscope. My experimental work was confined to the removal of skin warts through a water medium. I soon convinced myself of the efficacy of this therapy, despite the absence of an air gap. I also tested my Nitze cystoscopes and found that they stood the test perfectly. They were not burned out and I could readily see what was going on at the end of the electrode though very rarely an insignificant variation in the intensity of the light occurred.

Through the courtesy of Dr. A. G. Gerster, I was able to try out this new method in an inoperable tumor of the bladder in a woman of 81. In a second case, that of woman of 66, I employed this method also. Both patients were troubled with hematuria. In the second case the bleeding was very active, while in the first case it was moderate when the treatment was begun. As my experiences in these cases were highly satisfactory, I hasten to lay them before the profession, that others may avail themselves thereof.

TECHNIC, ETC.

Instruments—1. I employed the Oudin current derived from a Wappler machine, placing the rheostat vertically so that one-half the resistance was thrown into the circuit. The spark gap in the muffler was approximately 1/10—1/8 inch.

2. Nitze, double-catheter cystoscope was used. In one catheter tunnel, I placed the electrode introducing it just as one introduces a catheter while to the other catheter tunnel I attached a tube for irrigation.

3. The electrode was a simple 6-ply cable of copper wire thoroughly insulated with rubber and cut off squarely at the vesical end. It measured No. 6 French and was made for me by the Wappler firm.

Application—The applications were made directly to the growth, the electrode being pushed a short distance in among the villi under

* Reprinted from *J. A. M. A.*, 54: 1768–1769, 1910, with the kind permission of the publishers.

Transurethral fulguration of bladder tumors, introduced in this brief note, rapidly became accepted treatment and the principle was soon applied to other areas. The success of the transurethral approach for fulguration, moreover, encouraged the development of transurethral prostatectomy. A. B. G.

the guidance of the eye and then the current was turned on for fifteen to thirty seconds at various points. The bladder was distended with distilled water. Experience may show that some other medium is preferable in view of the fact that ionization with magnesia appears particularly effective in removal of skin papillomata.

EFFECTS AND RESULTS

The immediate visible effects are very striking. No spark is seen even when the full current is thrown on without any resistance. While the current is on gas is generated quite freely and is seen bubbling out of the growth. If the point of application is superficial we can readily see a blanching of the tissues about the point of application; and at the spot where the electrode's point rested, the tissues are blackened—carbonized. As the electrode is withdrawn from the growth, very frequently it is found to be adherent to the villi, and as it is pulled on, the whole tumor moves with the electrode, which finally comes away with a piece of the tumor well baked to its vesical end.[2] This is only rarely followed by bleeding and a reapplication of the current at the same spot controls this bleeding. The great heat generated melts the insulating rubber at the end of the electrode so that one has to cut it off squarely from time to time, to prevent the wires from protruding freely and injuring the bladder wall.

In the second case the very first application of the current controlled the bleeding to such an extent that cystoscopy, which had been almost impossible, owing to the excessively rapid clouding of the medium from the arterial bleeding, became fairly easy. Eight applications at one sitting to various parts of the growth, aggregating in all four minutes, controlled the bleeding. In the first case, the hematuria was equally well controlled, but the result was less striking than in Case 2, in which the severe hemorrhage ceased at once and intensely bloody urine gave way to normal yellow urine.

Such applications of fifteen to thirty seconds seem to cause a very well-marked necrosis, which is in part due to the heat engendered. Other factors probably contribute to the final result. How much ionization, electrolysis and other factors contribute, I cannot state as yet. By making applications at eight to twelve different points in the two large tumors treated, a total necrosis of all the villous outgrowths followed with absolute cessation of hematuria. Gradually during three to five weeks the dead tissue separated from the healthy and the tumors were expelled in small masses, as the mucous membrane gradually grew in around the base of the dead tissue. No ulcers were visible at any time.

The treatment caused no more discomfort than an ordinary cystoscopy. The bladder mucous membrane was but little affected by the application through some congestion and trigonitis developed in the vicinity of the growths.

At some future date, I shall report these cases in full, which is hardly necessary for this preliminary note.

2. These fragments have been used for microscopic examination.

A Study of the Endocardial Lesions of Subacute Bacterial Endocarditis*

With Particular Reference to Healing or Healed Lesions; with Clinical Notes

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DURING the last ten years I have been enabled to study an unusually large number of cases of subacute bacterial endocarditis. Particularly in the last few years I have become impressed with the great frequency of the condition (in 1911 I saw 27 cases). Altogether I have had the opportunity of studying at least 89 cases. Blood cultures were made in 75 of 78 active cases—by this I mean cases in what I call the bacterial stage. The other 3 cases were typical clinically; 1 passed out of observation and the other 2 died, autopsies not being obtainable.

Organisms were recovered from the blood of 73 of the 75 cultured cases. In 71 cases the cocci characteristic of the disease were obtained,[1] and in 4 the influenza bacillus. The symptoms and lesions found in the latter group were practically the same as those found in the former, except that thus far the glomerular lesions in the coccus cases have not been discovered in the kidneys of the influenzal cases that have come to postmortem examination.

[1] Libman and Celler, AMER. JOUR. MED. SCI., 1910, cxl, 516, and Trans. Assoc. Amer. Phys., 1910.

There were 2 supposedly active cases in which the cultures were negative. In the former five cultures were made in a variety of ways in our laboratory, and one in another, all being negative. This patient died at another hospital, and characteristic lesions were found in the heart, with cocci in the vegetations. These cocci were not studied, but I have no hesitation in putting down the case as one belonging in the group of subacute bacterial endocarditis. In the other case two cultures were made, neither very satisfactory. This case died and there was no autopsy made, but the clinical picture was definite.

The term "subacute bacterial endocarditis" I have adopted instead of the older terms: "chronic ulcerative endocarditis," "chronic malignant endocarditis," "chronic infectious endocarditis," and "endocarditis lenta" (Schottmüller). I call all cases of endocarditis already proved to be due to bacteria (rheumatism is not so proved) "bacterial endocarditis," and divide the cases into "acute," "subacute," and "chronic," according to their clinical course. When the causative organism in a given case is obtained, I insert

* Reprinted from *Am. J. M. Sc.*, 144: 313–327, 1912, with permission of the publishers. To conserve space it has been necessary to delete the eleven brief case reports cited, almost all bibliographic references and some portions of the text.

Emanuel Libman devoted much of his early career to developing the technics and application of blood culture. His publication in 1906, "Experience with Blood Cultures in the Study of Bacterial Infections," was an important contribution to this field. Out of this grew his interest in bacterial endocarditis, of which he was a life-long and foremost student, and later in abacterial "atypical verrucous endocarditis" (Libman-Sacks). The present paper introduces the terms "acute" and "subacute bacterial endocarditis" now in universal use and as evidence of his clinical acumen calls attention to the café-au-lait color and many other clinical features of the disease. The paper has renewed timeliness because the characteristics of healing or healed infection, notably renal impairment, play such an important role after treatment with antibiotics. A. B. G.

the name of the organism for the word "bacterial," thus, "acute streptococcus endocarditis," etc. Many of the cases that belong in the group with which we are dealing last only four to six months, and are therefore certainly subacute and chronic. Some may prefer to apply the term "chronic" to the cases that last over one year.

Besides the 77 active cases, we have observed 11 cases, which I believe belong in the group of subacute bacterial endocarditis, but in which the lesions found were in a healing or healed stage, and in which the lesions were found free from pathogenic bacteria. In 10 of the cases, blood cultures were made during life (in a few anaërobically), and no bacteria were found. In 1 case as many as nine cultures were made during a period of ten months, all with negative results.

There are many viewpoints from which such large material as I have at my disposal could be presented. I shall attempt in the present communication to show that the lesions found in the cases of subacute bacterial endocarditis in which the mitral valve is involved are quite characteristic. I hope to demonstrate that there are three stages in many cases of this disease: the bacterial, the bacteria-free healing, and the bacteria-free healed stage. I should also like to point out that at least some of the cases which we have been wont to call "chronic endocarditis with fever" are examples of the healed or healing forms of subacute bacterial endocarditis, for healing from a bacteriological or bacteriological and pathological standpoint does not necessarily mean recovery from a clinical standpoint.

When the mitral valve is involved in cases of subacute bacterial endocarditis (and it is involved in the larger number of cases) there is a tendency for the vegetations to spread up on the left posterior wall of the auricle more than on the valve itself. Often the chordæ tendineæ attached to the posterior flap are covered to a greater or lesser extent by vegetations. Nearly always the anterior flap is also involved, and here the vegetations tend to grow down over the chordæ tendineæ, the involvement of the latter being often extensive. Not uncommonly the chordæ are ruptured, the torn ends at times being massed together by vegetations at the edge of the flap, or the lower ends may be found lying loose near the papillary muscles. The vegetations are yellowish, greenish, pinkish, or reddish in color, and vary much in size in different cases. As they grow older they become firmer and assume a more grayish color.

When the aortic valves are involved the lesions are not usually characteristic and their extent is most variable. There may be only a small vegetation on one or more of the flaps of the valve. On the other hand, there may be enormous green masses that must block the orifice to a greater or lesser extent. The vegetations have a tendency to extend down over the endocardium at the position of the septum membranaceum and over the ventricular aspect of the aortic flap of the mitral valve and down over the chordæ tendineæ. At times they have a stalactite-like appearance. There may develop an aneurysm of the aortic flap of the mitral valve. Ulceration of the aortic valve at times occurs; ulceration of the mitral flaps is rare.

A study of frequency of involvement of the valves, the left auricle, and the chordæ in the hearts from 34 cases of the disease in which the blood cultures were positive during life was made with the following results:

Auricle, mitral valve, and chordæ	17	cases
Auricle, mitral valve, chordæ, and aortic valve	5	"
Auricle and mitral valve	2	"
Mitral valve and chordæ	1	"
Aortic valve only	3	"
Aortic valve, chordæ, and aortic flap of mitral	4	"
Mitral valve, chordæ, and aortic valve	1	"
Auricle, mitral, and aortic valves	1	"
Total	34	cases

The auricle was involved 25 times, the mitral valve 27 times, the chordæ 28 times, and the aortic valve 9 times. The frequency of the involvement of the chordæ and auricle is very striking.

The lesions which we consider so characteristic of this group of cases we have not found in a large series of cases of acute endocarditis (58 in number) due to the streptococcus, pneumococcus, and the staphylococcus. In our own cases of acute gonococcus endocarditis we have not met with similar lesions. But I have, through the kindness of Drs. Asch and Humphries, of the German Hospital, seen one case of gonococcus endocarditis, apparently of only three weeks' duration, in which the lesions resembled those seen in the group of cases under discussion. The symptoms seen in the typical cases of subacute bacterial endocarditis were not present nor were the characteristic glomerular lesions found in the kidneys.

And as, in the group of 34 cases just tabulated above, only 1 was due to the influenza bacillus and the other 33 to the endocarditis coccus, the lesions must be considered characteristic of infection by these cocci. There are occasional notes in the literature on such lesions in cases of bacterial endocarditis, particularly by Osler and Harbitz. These will be discussed in the fuller paper which will appear later.

After I had made these observations I found (in 1909) lesions in the heart of a man in whose case a clinical diagnosis of chronic nephritis and uremia had been made, which appeared to me to represent the healed form of the lesions I had previously found in cases of infection by the endocarditis cocci. There were extensive lesions on the wall of the auricle in a state of organization, and the chordæ tendineæ attached to the anterior flap were found torn, thickened, fibrous, and in part calcareous. Bacteria were not present. My opinion that these were the healed lesions of subacute bacterial endocarditis (in all probability due to the cocci) was confirmed recently by Dr. Baehr's studies of the kidneys in all the material we have in the museum from cases of bacterial infection of the heart valves.

Dr. Baehr investigated particularly the glomerular lesions described by Loehlein in cases of endocarditis due to the Streptococcus viridans of Schottmüller, which organism seems to correspond to the cocci found in our subacute cases. Dr. Baehr studied the kidneys of 25 cases of endocarditis due to the endocarditis coccus ("Streptococcus viridans" or "Streptococcus mitis") which were still in the bacterial stage, and found the lesions described by Loehlein in 23. In 2 other cases, 1 an infection by the influenza bacillus and the other the case of gonococcus infection before mentioned (with rather acute course, but with endocardial lesions like those in the coccus case), the lesions were absent. In the kidneys of 54 cases of endocarditis due to the ordinary streptococci, staphylococci, the pneumococcus, and the gonococcus no such lesions were found. The lesions must therefore be considered characteristic of infections of the heart valve by the endocarditis coccus.

In the kidneys of the case which I have just mentioned, which I believed at the time the case came to postmortem examination represented a spontaneously healed case (from the bacteriological and pathological standpoints), the characteristic glomerular lesions were found. After observing this case I again looked over my collection of hearts from cases of subacute bacterial endocarditis, and was surprised to find how often there is a tendency to healing of at least part of the lesions. In a number of cases I found that the upper part of the auricular lesion was already organizing or was organized, while other parts of the lesions were active and filled with bacteria. I also found a tendency to calcareous infiltration in chordæ tendineæ which were covered by vegetations. And even in extensive vegetations on the aortic valve, which on the whole appeared to be quite active, marked calcareous deposits could be found. It was of the greatest interest to observe the transitions between the lesions present in active cases and the lesions we were beginning to find in the cases which I believed to represent healed cases of the disease in question. Including the case mentioned above (Case 1) we have now studied the lesions in 11 cases in the last-mentioned group.

We have then before us 11 cases in which we have every reason to believe that we are dealing with cases in which patients who had a subacute bacterial endocarditis overcame the infecting agent without their having been seen at a time when the infection was still active. In 1 poorly staining cocci were still seen in small numbers in part of the lesions. In 7 of the cases the mitral valve was involved in a way seen practically only in subacute bacterial endocarditis. As 95 per cent. of our active cases were found to be due to the endocarditis coccus, it is fair to assume that nearly all of the 7 cases were due to the coccus. Besides which we have further evidence in the presence of the characteristic glomerular lesions in all of them.

One case had a calcareous mass on the aortic valve and involvement of the chordæ tendineæ in characteristic fashion. The latter lesion is in itself suggestive, and besides this typical glomerular lesions were found.

We have left 3 other cases in which only the aortic valve was involved and in which large calcareous lesions were found. In all of these we have the proof afforded by the presence of the glomerular lesions that they were almost surely the result of infections by the endocarditis coccus. And I have pointed out that there are transition stages to these lesions in cases which still have the cocci in the blood during life and in the lesions.

It is of interest to note in the cases with aortic involvement (calcareous masses on the valve) that aneurysms are frequent and that they are

of a different type from the bacterial embolic type. One finds aneurysms of the sinuses of Valsalva, the heart wall just below the aortic valve, the aortic flap of the mitral valve, and in the peripheral arteries. All except the last seem to be due to impact by the calcific material on the valve. They are all smooth walled. The peripheral aneurysms seem to be due to the traumatism to the wall inflicted by a piece of lime whipped off from the valve. Some years ago I pointed out that such non-infective embolic aneurysms actually existed.

The question will now be asked, How often does one see a case of subacute bacterial endocarditis in which blood cultures have been positive, become bacteria-free and go on with symptoms due to the changes left in the heart or recover completely? As regards this point, our own experience has been that nearly all the cases in which we found bacteria in the blood and which we could follow went on to a fatal termination, with bacteria still present in the blood. In but few cases did the blood cultures become negative; these patients also soon succumbed. In one case of infection by the influenza bacillus five blood cultures were positive and four later ones were negative. This patient died a couple of months after leaving the hospital, or about four months after the cultures became negative. He left the hospital quite anemic, and died of exhaustion and decompensation. An autopsy was not permitted. Our experience coincides with that of those who have seen large numbers of these cases.

It is curious in view of the facts just stated that there should exist so many cases which must have had a bacterial infection, have recovered from the infection, and have certain clinical pictures from the changes brought about during the infective period. We must assume that in these cases the period of bacterial infection was very short as compared to the cases which we see with bacteria in the blood or very short and very mild. When one sees cases of the disease with bacteria demonstrable in the blood go about for weeks with hardly any symptoms it is not difficult to believe that some patients with a mild or short infection may not feel sick enough to ask for medical attention or present such mild clinical pictures that they are not put to bed. That the infection in such cases is a shorter one is also suggested by the study of the glomerular lesions. They were found to be much more abundant in cases in which cocci had been found in the blood than in those in which they were never demonstrated.

As far as the data which I have thus far at my command go they indicate that the cases with healing or healed lesions present the following clinical pictures:

1. They go on to have a nephritis and die of uremia.

2. They present the picture corresponding to what we have been wont to call "chronic endocarditis with fever" (that is they have a valvular lesion, more or less fever from time to time, usually low, occasional petechiæ, occasional joint symptoms, and embolisms). Some of these cases closely resemble cases in which bacteria are demonstrable in the blood. The differences will be discussed when I have more material. Some of these patients are pale and some more or less pigmented (see below).

3. Some of these cases present a clinical complex that appears to have been entirely overlooked. The striking feature is a peculiar diffuse brown (sometimes quite dark) color of the face. The rest of the body may show some pigmentation. There is evidence of a valvular lesion, there is more or less anemia, usually a palpable spleen, and usually also tenderness of the lower sternum. The patients feel weak and do not sleep well. Petechiæ occasionally occur. There is temperature from time to time, but usually low. Erythrocytes are found in the urine in some of the cases. The subsequent history of such cases is not yet known; one case died with symptoms of cerebral embolism. I wish particularly to emphasize the curious change in the color of the face. It will, I am sure, be of great importance in the recognition of some of the cases with healing or healed lesions. Since I have observed it in such cases I have looked for it in cases with bacteria in the blood. And now, to my surprise, I find that while the faces of most of the cases are sallow, or of a rather white color, some develop a certain amount of brown or *café-au-lait* color.

4. They may go on with more or less anemia, and suffer from that and from decompensation.

I would like now to note a few of the important symptoms that occur in the bacterial cases and state what my experience is as regards them in the cases in which the infection has been overcome:

1. Fever: This is found in all of the non-bacterial cases that we have observed, but it is a less marked feature and the temperatures are

low for much longer periods. In an earlier paper I have drawn attention to the fever which occurs in cases of chronic endocarditis without demonstrative bacteriema. At that time I made the following remarks: "There are many cases of chronic endocarditis with fever without demonstrative bacteriemia. In some cases causes for the fever may be found elsewhere in the body. If no cause can be found the acute symptoms may be due possibly to organisms not to be cultivated by our present methods. I have suspected that in some cases with irregular fever, at times high, and recurring from time to time, the temperature may be due to the discharge into the blood current of bits of thrombotic masses or old vegetations." Bock has recently shown that fever can be produced experimentally by the injection into the blood stream of bacteria-free, chemically indifferent particles.

2. Splenic Enlargement: This symptom seems to persist in the non-bacterial stage. I have reason to suspect that occasionally when the spleen is very large, the clinical diagnosis may appear to be a splenic disorder plus chronic endocarditis. In the bacterial stage, it is well known that the splenic enlargement may be so marked that such cases have been mistaken for cases of Banti's disease or splenic anemia.

3. Pains: These may be just as severe in the bacteria-free cases; the same holds true of joint pains.

4. Painful Cutaneous Erythematous Nodules: These were not observed in the bacteria-free cases except in one case, in which they were a prominent feature during the early period of the observation.

5. Sternal Tenderness: This symptom, on which I lay much stress, is equally frequently met with in both groups of cases. It even seems to be a more marked symptom in the bacteria-free cases. As I have stated in an earlier publication, sternal tenderness may be found even when the hemoglobin is not markedly reduced.

6. Petechiæ: These occur in the bacteria-free cases, but are not as abundant and do not occur so frequently. Purpuric eruptions seem to be a feature rather of some of the bacteria-free cases.

7. Hematuria: This subject needs further investigation. Erythrocytes were found in the urines of those cases of the bacteria-free groups in which they were carefully looked for. Gross hematuria—that is to say, smoky urine—I remember to have seen only once in the cases in the bacteria-free group, and it occurred in that case only during the early part of the period of observation.

Other symptoms, such as the sweats, the blood changes, the gastrointestinal phenomena, etc., will be discussed when more data are available. The facts that I have given show the close resemblance between many of the features in the two groups of cases. It is important that we can recognize at least some of the bacteria-free cases definitely. It will be of great value to search for such cases and to make studies of the serum in them. Complement fixation investigations carried on in connection with such cases may enable us to determine the exact status of the cases classed as chronic rheumatic endocarditis. We may be able to ascertain whether there exist cases that have had the bacterial infection and have completely recovered, being left with the original valvular lesion due to rheumatism.

It will finally be of interest to glance at the literature on the subject of healing of the lesions of subacute bacterial endocarditis. I shall take up at the present time mainly the experience of authors who have had the advantage of having blood cultures made in their cases. I shall not go into the question of the possibility of the healing of acute endocarditis; Herrick has discussed that subject fully.

Litten, Leyden, Osler, and Rosenow do not record any experiences with healed cases. Leyden believed that it was possible for "ulcerative" endocarditis to heal. He evidently had instances of subacute bacterial endocarditis among the cases he studied, but none with healed lesions.

Harbitz, in the report of his admirable investigations on endocarditis, discusses lesions that he found in 10 cases that he believes were related to "chronic infectious endocarditis," and in which the lesions were in a healing stage. He says that he did not succeed in obtaining bacteria in these lesions, but the anatomical picture, "the extension to the walls of the auricle and ventricle, the excrescences on corresponding parts of two adjacent flaps, the tearing of chordæ tendineæ," etc., was quite characteristic. These cases ran a long course, at times associated with subacute nephritis. In one case of this group in which the cultures at the autopsy were sterile, Peter Holst obtained two weeks before death a "white staphylococcus" in the blood. In a few cases indistinct groups of organisms were found in sections and smears made from vegetations,

and the cultures were negative. These observations of Harbitz are the most definite hitherto recorded.

It will be noted that the observations on the healing of subacute bacterial endocarditis are rather few in number. From the pathological standpoint those of Harbitz are the most illuminating. From the standpoint of healing in a clinical sense the observations of Latham and Hunt and Reiche and Jochmann are important. It seems remarkable that the cases that have spontaneously become bacteria-free have hitherto escaped detection.

I believe I have brought forward sufficient evidence to prove that subacute bacterial endocarditis is a disease in which healing can occur from the bacteriological, pathological, and clinical standpoints, although the evidence of complete recovery from the clinical side is still very meagre.

It is a pleasant duty for me to express my gratitude to Drs. Rudisch, Meyer, Brill, and Manges, the visiting physicians to Mount Sinai Hospital, for their kindness during many years in permitting me to make studies on their cases. The clinical data are mainly derived from the cases in the service of Dr. Rudisch and from cases which a number of physicians permitted me to observe in their practice. I wish to add that it would not have been possible to complete the bacteriological and pathological studies as far as they have been carried without the enthusiastic assistance of the various members of the laboratory staff for the last ten years.

Blood Transfusion by the Citrate Method*

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IN a preliminary communication[1] I reported on a new method of performing blood transfusion with the aid of sodium citrate. This short report dealt mainly with the results of animal experiments. Since that time I have applied the citrate method in twenty-two blood transfusions on eighteen patients. I have thus been able to collect in a comparatively short time (about two months), partly with the kind aid of the staff of Mount Sinai Hospital, a sufficient number of cases to test the clinical value of this new and very simple method of blood transfusion. The object of this paper is to describe these clinical experiences, in the hope that the profession may be induced to give this method a trial on a larger scale and form their own opinions as to its clinical value.

HISTORY

The current idea, that transfusion of blood for therapeutic purposes dates back only a few decades, is an erroneous one. In fact, the history of blood transfusion (quoted from Amstel) takes us back as far as 1667, when Denis conceived the idea of blood transfer and used it successfully on the human being. The first one to make use of blood transfusion on a larger scale was Blundell, who reported four cases; two of these ended fatally, but the other two were successful. The largest amount of blood used in these cases was 480 cubic centimeters. It is interesting to note that the use of blood transfusion in puerperal fever dates back as far as 1829, although it has recently been again suggested by different authors. It would go far beyond the scope of this paper to give a detailed review of the extensive work in this field in the nineteenth century, although it is a most interesting study. Transfusion was used over fifty years ago in carbon monoxide-poisoning, eclampsia, leukæmia, etc. Toward the end of the last century it was gradually abandoned in favor of saline infusion. It is only since Carrel's masterful work in blood-vessel surgery that transfusion was taken up again on a large scale, especially in this country. The reason that Carrel's work was such a great step forward is that his method afforded for the first time a safe way of transferring blood from donor to recipient without the risks and dangers of coagulation. The artery-to-vein anastomosis was for a great many years the method of choice in blood transfusions. Its great technical difficulties were obviated to some extent by the use of certain cannulas (Crile, Elsberg, etc.). Later vein-to-vein anastomosis for transfusion was substituted as a more simple and quite as satisfactory a method as artery-to-vein anastomosis.

The greatest objection to the method of direct transfusion, as the anastomosis method is usually called, is not its minute and rather cumbersome technique, but the impossibility of ascertaining the exact amount of the transfused blood. It is obvious that this is a serious objection. That is one of the reasons why in such a short time the syringe method of Lindeman became so popular that it practically did away with all the different direct methods. The syringe method requires for its proper execution three or four people, who must work together with great precision. Furthermore, the method is an expensive one. The usual set consists of twelve twenty-cubic-centimeter record syringes; and if not handled very carefully they break easily, especially during the process of boiling.

[1] Med. Rec., 1915, Jan. 23.

* Reprinted from *Surg., Gynec. & Obst.*, 21: 37–47, 1915, with the kind permission of the publishers. In order to conserve space it has been necessary to delete the author's condensed reports on eighteen cases of transfusion, most of the bibliographic references and brief sections of the text.

This paper had an important effect in encouraging the more general use of blood transfusions, with sodium citrate as an anticoagulant in the concentration here suggested, and may have indirectly stimulated solution of many of the other problems in the way of safeguarding and simplifying the transfusion of blood. A. B. G.

Unger has lately constructed a very ingenious apparatus, which is an improvement on Lindeman's technique. Its essential feature is that the aspiration and injection of the blood is regulated by a double-way stop-cock. In this manner the team-work between the two men working on the donor's arm and the recipient's arm respectively is replaced by a piece of machinery and the prompt working of aspiration and injection of the blood is assured.

The fundamental difference between all methods of transfusion heretofore suggested and the citrate method which shall be described in detail in this paper is based on the following considerations: All the older methods consider the coagulation time of the blood, which normally occurs in about five minutes after the blood has left the vessels, as a *noli me tangere*. They all tried to adapt their methods to this well-known fact. That is the reason why the vessel anastomosis met with success. The adaptation of endothelium to endothelium is, as we all know, a safe way of preventing coagulation. The danger of coagulation makes the use of a set of small syringes (20 ccm.) imperative for the syringe method, instead of one or two large syringes (200 to 300 ccm.), and thus complicates the method materially.

Any transfusion, in which the normal coagution time of the blood is considered as an unalterable factor, is apt to be difficult and apt to require a great deal of personal experience and skill. Must we accept this coagulation time as an unchangeable law? Might it not be possible to inhibit the danger of the clotting of the blood during its transfer without diminishing the clinical value of the transferred blood for the recipient? This was the problem to be worked out, and it seemed to me that this problem would be worth a thorough and careful investigation. If solved, blood transfusion, which so far has given only good results in the hands of a limited number, would be changed from a very complicated and difficult method to one of greatest simplicity. Special clinical skill and experience for this work would no longer be required, no haste would be necessary in the performance of transfusion; in short, blood transfusion would be technically as easy as an ordinary saline infusion.

EXPERIMENTS

The problem, then, was to find a chemical substance which would retard the coagulation of the blood for at least thirty minutes, so as to guarantee a safe transfer of the blood without any haste. Furthermore this substance had to be conditionally atoxic, so that large transfusions of blood (up to 1500 ccm.) could be performed with perfect safety.

Several anticoagulating substances are well known in physiological chemistry and have been used extensively in the laboratories: hirudin (leech extract), sodium citrate, sodium oxalate, peptone, glucose, etc.

My work was commenced by testing hirudin. Hirudin has been used quite extensively in Germany in the treatment of eclampsia. Engelmann reported 14 cases, in which he used up to 0.3 grams of hirudin intravenously without any toxic symptoms. We know from the work of Friedrich that 0.1 gram of hirudin prevents 750 ccm. of blood from coagulating. From a series of experiments on blood received from patients, where a phlebotomy was indicated, it became apparent that the smallest dose of hirudin applicable for our purpose was 0.03 grams of hirudin to 200 cubic centimeters of blood. For the average transfusion of 1000 cubic centimeters we would then use 0.15 grams of hirudin, only half of the dose injected by Engelmann in eclampsia. Preliminary to using hirudin on the human being, I injected up to 0.1 gram of hirudin intravenously into some medium-sized dogs. One dog died four hours after the injection, but we thought this might be due to an overfilling of the circulatory system, as we had diluted 0.1 gram of hirudin with 100 cubic centimeters of saline solution. The other dogs (0.1 gram of hirudin diluted in 20 cubic centimeters of solution) showed no ill effects (after having been observed five days). I then used hirudin on a patient who had an inoperable carcinoma of the stomach (exploratory laparotomy). As she needed a saline infusion the day following the operation, I added 0.1 gram of hirudin (Sachsse) to 500 ccm. of saline solution. The symptoms following this infusion were most alarming; cyanosis and precordial pain set in immediately, followed by a severe chill. Her pulse became almost imperceptible; she was in a precarious condition for over thirty-six hours and recovered only very slowly from this severe reaction. This experience naturally ended further trials with hirudin.

After the failure of my experiments with hirudin I took up experiments with sodium citrate to test its possible usefulness for our

purpose. When I began my experiments with the citrate method I looked over the current literature, but was unable to find any reference to any work done along these lines. After my work had come to a successful conclusion I found that a paper published by Hustin[1] in May, 1914, had escaped my notice. It appears from this paper that the priority, not only for taking up this problem in a series of animal experiments, but in applying it successfully in a case of human blood transfusion, belongs to Hustin, though his method, as we shall see later, limited its usefulness to small transfusions.

Again, as in my experiments with hirudin, the first series of investigations was carried out with the object of finding the smallest dose of sodium citrate required to keep the blood from clotting for thirty minutes. We* took ten test tubes containing 0.1, 0.2, 0.3, etc., up to one cubic centimeter of a 10 per cent solution of sodium citrate. A dog was narcotized and 10 cubic centimeters of blood, taken from his jugular vein, poured into each of the test tubes; another test tube, not containing any citrate, was filled with 10 ccm. of blood. The blood in the first test tube, containing 0.01 sodium citrate to 10 ccm. of blood, clotted just as quickly as the blood in the control; namely, in about five minutes. The blood in the next tube (0.2 per cent) did not clot for two days. On the third day this tube, as well as the next one (0.3 per cent), showed a soft clot, whereas the rest of them (0.4, 0.5 per cent, etc.) were still fluid. These experiments were repeated at different times, always with the same results. The interesting fact elicited from these experiments was that sodium citrate mixed at the rate of 0.1 per cent does not change the coagulation time of the blood, but that a mixture of the sodium citrate with blood at the ratio of 0.2 per cent prevents the blood in the test tubes from clotting for three days. The quantity of citrate needed for this object lies just below 0.15 per cent, but in order to be on the safe side it seems advisable to fix the ratio needed for our purpose as 0.2 per cent. Exactly the same rulings were proved to hold good for human blood.

The next question to be answered was in reference to the toxicity of sodium citrate. If the citrate method was to compete with the older transfusion methods, it had to be applicable to transfusions as large as 1,500 ccm. It was not sufficient to prove that small quantities of blood (that is 200 ccm.) could be transfused with this method without risk to the patient. I am sure that hirudin would have answered the problem if we had expected to transfuse only small quantities. In a great many cases, however —in fact, in the great majority of blood transfusions—it is necessary to transfuse 700 to 1,000 cubic centimeters and sometimes more. The whole method would have only a limited field of usefulness, if we could not use it for large transfusions with perfect safety to the patient.

Sodium citrate can be used with perfect safety at the ratio of 0.2 per cent. Three hundred cubic centimeters of blood were removed from a dog's carotid artery, mixed with sodium citrate (0.06 gram) and reinjected into the jugular vein of the same dog. No ill effect was noticed during the observation time (two weeks). This experiment was repeated a few times with exactly the same result.

On the other hand, sodium citrate is only conditionally atoxic, which means that we cannot inject any unlimited quantity of sodium citrate into the vascular system without running a great risk. This is proved by the following experiments, which differed from those just described only in so far as the dose of citrate was increased. I took a dog weighing 11 pounds and mixed the blood with 15 ccm. of a 10 per cent solution of sodium citrate. The dog died almost instantaneously. This experiment was repeated twice with exactly the same fatal result. It follows that we have to consider 1.5 grams of sodium citrate as a fatal dose for a dog weighing eleven pounds. Fifteen grams would then be a fatal dose for a patient weighing one hundred and ten pounds. As even 10 grams would nearly reach the fatal limit, it would be utterly impossible to apply this method, if the 1 per cent ratio, as suggested by Weil,[1] would really present the smallest dose of sodium citrate necessary for our purpose. The whole method would then be applicable only for small transfusions (Weil has injected 250 ccm. of blood mixed with 2.5 grams of sodium citrate), and would thus have a rather limited field of usefulness. Hustin also thought, that 0.2 per cent was too small a dose to keep the blood from clotting, and therefore mixed the citrated blood with the

[1] Hustin. Ann. et Bull. Soc. Roy. de Soc. Med. et Nat., Bruxelles, 1914, No. 4, 104.

*Dr. George Bachr very ably assisted me in these experiments.

[1] Weil. Discussion, N. Y. Acad. Med., December 17, 1914; J. Am. M. Ass., 1915, lxiv, 425.

same amount of saline solution, adding some glucose, which is a well-known means of retarding coagulation. Here again the adding of an equal amount of saline solution to a given quantity of blood would limit its application to small transfusions (Hustin transfused only 150 ccm. in the one case referred to above); it would not be practical from a clinical standpoint to add 1,000 ccm. of saline solution to a blood transfusion of 1,000 ccm.

The third point of interest, in addition to the questions of dose and toxicity, is the question of the coagulation time of the recipient's blood after the transfusion. We have seen that blood mixed with 0.2 per cent sodium citrate does not clot outside the body in two to three days. If this fact would hold good after the injection of the citrated blood into the recipient, the older, though more complicated methods, would have clinically such an advantage over this method that this paper need not have been written. However, confirming a statement made by Weil at the New York Academy of Medicine, animal experiments and experiences in human blood transfusions show, the most interesting fact, that the same citrated blood which does not coagulate outside the body in two days, does not retard the coagulation of the general blood volume. On the contrary, the coagulation seems to be temporarily hastened. Three hundred cubic centimeters of blood were taken from a dog, mixed with citrate (0.2 per cent) and reinjected. The time for the coagulation of the normal blood taken before the experiment was started was five minutes. Blood taken from the same dog three minutes after the reinjection of the citrated blood showed that coagulation occurred after only ten seconds. A third test taken three minutes later showed the same result as the second.

This question certainly would lend itself to a further and more detailed investigation. We have not been able to find in our human blood transfusions any marked changes of the coagulation. The marked hastening of the coagulation of the blood, which we found in the dog experiment, does not seem to hold good, at least not to that extent, for human blood. And if it does, it is of such a short duration that it escaped our notice, as most of our coagulation time tests were taken a few hours or the day after the transfusion. There certainly does not exist, however, any marked retarding of the coagulation after a citrate transfusion, a fact which is of the utmost importance for the question of blood transfusion by the citrate method.

TECHNIQUE

Before describing the technique of blood transfusion by the citrate method, I would like to say a few words about the donor, as I consider the proper selection of a suitable donor of the greatest importance. The donor ought to be a strong, husky individual with prominent veins. It is not advisable as a rule to use members of the patient's family, as they are, often, naturally very excited about the condition of the patient and do not stand the loss of blood as well as a professional donor, who offers his blood for a monetary consideration and has no personal interest at stake. I have seen donors who have given up large quantities of blood for transfusion at short intervals—ten to twelve times inside of twelve months. Though no fixed laws can be laid down, it is advisable to refuse donors who have been repeatedly used. It is needless to say that all the preliminary tests (Wassermann, agglutination, hæmolysis, etc.) must be done just as well with the citrate method as with other methods. There is no doubt that the procuring of a donor and the necessary blood tests make transfusion impossible, when needed on the spur of the moment. In exceptional cases (see Case 16) transfusion may be done without the test; as a rule it is certainly wise to wait for the tests, which can be done in a few hours.

The technique of the citrate method is so simple that it can be dealt with in a few words. The donor is put on a table, a tourniquet applied to the arm, and the vein punctured with a cannula. The blood is received in a sterile graduated glass jar (500 ccm.) containing 25 cubic centimeters of a 2 per cent sterile solution of sodium citrate at the bottom. While the blood is running into the glass receptacle, it is well mixed with the citrate solution by means of a glass rod. After 250 cubic centimeters of blood have been taken another 25 cubic centimeters of citrate solution are added. If less than 500 cubic centimeters of blood are taken (i.e., in infants), the amount of citrate solution added to the blood is reduced accordingly. In cases where we expect to take more than 500 cubic centimeters of blood we have another glass container (500 ccm.) ready to be used in exactly the same manner. The glass jar containing the blood is then put aside and covered with a towel to safeguard against contamination. I have not

found it necessary to immerse it in hot water or surround the jar with an asbestos covering. The blood is then taken either into the recipient's room or the recipient is brought into the operating room. I consider it a great advantage that this method does not require donor and recipient to be in the same room; this lessens the physical shock for the whole procedure for the patient. In fact the donor's blood may be collected in the laboratory or office and carried to the patient's bedside (Kaliski).

Another very great advantage of the citrate method is that as there is no connection between the donor and recipient the donor is safeguarded against contagion of any disease or infection which the patient may have.

The recipient's vein is then punctured or exposed by a small incision; the cannula is introduced and attached to a salvarsan flask or a glass funnel. It is advisable to fill the rubber tubing connection between flask and cannula with some saline solution, so as to prevent air from getting into the circulation. After the connection is made the blood is poured into the salvarsan apparatus. In order to prevent sudden overloading of the circulation it is advisable (especially in larger transfusions) to stop the flow of blood from time to time by compressing the rubber tubing. After the blood has been injected the cannula is removed and the transfusion is thus ended. The whole procedure can be performed with the greatest ease and without any hurry, because the citrated blood, as we have seen above, can be kept for two or three days in the glass jar without danger of clotting.

It is rather immaterial what size needle we use for the injection of the blood; in children, for instance, we can use a very fine Goldenberg or Schreiber needle. But it is of the greatest importance for the successful application of the citrate method that we use a large size cannula in taking the donor's blood. I have lately punctured the vein with a Kaliski cannula (gauge 11. B. & S.), and thus collected 500 cubic centimeters of blood in less than five minutes. The shape and construction of the needle (Lindeman, Kaliski, Unger, etc.) are immaterial so long as one uses one of large caliber. I would like to warn against the use of needles of smaller caliber (for instance, 14 or 16), because if the blood does not shoot out of the vein, and comes out only drop by drop, the blood is apt to clot in the glass jar. If we use needles of sufficiently large caliber, we do not need syringes, which only complicate this method, and certainly are not to be considered as an improvement in the technique.

The 2 per cent citrate solution can be sterilized and resterilized without losing its efficiency. I selected a 2 per cent solution because it simplifies the calculation (30 solution to 300 blood). By varying the percentage one can easily reduce the quantity of solution to be added to the blood. It might be just as advisable, for instance, to add 50 ccm. of a 4 per cent solution to 1,000 ccm. of blood. I have had made up sterile glass tubes (like those for saline solution) containing 50 ccm. of the 2 per cent solution ready for immediate use.

CONCLUSIONS

The clinical material of this review of 22 citrate transfusions in 18 cases is comprised of the following cases: Inoperable carcinoma, 3 cases; preoperative transfusions, 3 cases; purpura hæmorrhagica and allied conditions, 5 cases; lymphatic leukæmia, 1 case; severe anæmia, 2 cases; gastric hæmorrhage, 2 cases; actinomycosis, 1 case; puerperal sepsis, 1 case. Out of these 18 cases 4 were transfused twice within short intervals.

All the points of clinical interest have been discussed in the records of the cases. However, I would like to dwell on some which are of importance, not only in regard to the citrate method but in reference to any human blood transfusion.

Some of the cases showed a rather marked polyuria lasting twenty-four hours, though I must say that this increased excretion of urine appeared only in a small percentage; none of the cases showed any macroscopical or microscopical changes in the urine. A marked rise of temperature was noted in 5 cases, 3 of which were accompanied by a chill after the transfusion. It is possible that some rises in temperature escaped our notice, as the patients were running septic temperatures before the transfusions. It is a well-known fact that chills following transfusion, or even simple saline infusions, occur rather frequently (Lindeman had 22 chills in a series of 62 cases). In our series chills were observed in three cases out of twenty-two transfusions.

A good indicator of an effective transfusion of blood is the automatic rise of the hæmoglobin after the transfusion. For instance, by a transfusion we raise the hæmoglobin of the patient from 20 per cent to 40 per cent. and we notice

during the following week that the hæmoglobin goes up automatically another 10 to 12 per cent. This rise of the hæmoglobin was noticed in a large number of our cases and is a proof of the good clinical value of the citrated blood.

The question of the coagulation time has been discussed above. If the hastening of coagulation after the injection of citrated blood, as apparent from animal experiments and some experiences on the human being, were to last any length of time, it would be of the greatest value in different hæmorrhagic conditions (especially hæmophilia). The shortening of the coagulation time is, however, of such a transitory nature, the clinical conditions existing before the transfusions are reëstablished so quickly, that we cannot expect any greater help for these diseases from the citrate method than from any other method of transfusion.

It would be very tempting to enter upon the broad question of the indications calling for blood transfusions. This paper, however, was written mainly to advocate a new method of transfusion, and a thorough investigation of these indications would go beyond its scope. Furthermore, Ottenberg and Libman[1] have taken up this subject in an admirable paper on "Blood Transfusions, Indications, Results, General Management," which will be published in the near future. Their paper, based on experiences in 212 cases of blood transfusions, dwells upon all the interesting factors of this subject. It must be considered as one of the most valuable publications in this field.

Transfusion of blood, as we have seen above, had a very varied career in our medical armamentarium. Though practically forgotten for nearly a century, it has been revived in the last decade, and on account of great improvements in the technique (uppermost among them the blood tests for agglutination and hæmolysis) transfusion is now to be considered a safe method, yielding excellent results in properly selected cases. The success of transfusions is most striking in profuse hæmorrhage (ulcer of the stomach and duodenum, ectopic pregnancy, typhoid and cholæmic hæmorrhages, etc.), in different forms of poisoning and in some hæmorrhagic conditions. It produces excellent and lasting results in cases of primary and secondary anæmia, whereas improvements following transfusions in different forms of leukæmia and pernicious anæmia are not as a rule of a lasting character. I think transfusion ought to be practiced much more than heretofore as a preparatory step in cachectic patients who are to undergo extensive operations. Operative shock seems to be a promising field, though the experiences of Ottenberg and Libman are not very encouraging. Though a great deal has been written on this subject in the last year, some of the indications for transfusion in sepsis and tuberculosis are still very questionable. If we approach the question of transfusion without too great an optimism on the one hand and without being overskeptical on the other hand, we are sure to make progress in this most interesting field. Transfusion is not a panacea for every disease, but it certainly has a wide field of usefulness.

I am well aware that this new method of transfusion has to be tested on a much larger scale before definite judgment can be passed upon it. However, I think that the reports given above are sufficiently encouraging to induce the profession to give this method a fair trial. I feel assured that the citrate method has come to stay. Clinically, it appears to be as good as any of the older methods, and at the same time it has the advantage of the utmost simplicity.

[1] Ottenberg and Libman. New York Academy of Medicine December 17, 1914.

Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation*

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ONE of the most striking clinical manifestations of chronic parenchymatous nephritis is the development of edema or anasarca. Its occurrence is intimately associated with a diminished elimination of salts and water, believed to be due to a reduced power of the kidneys to excrete these substances. Those who have had occasion to observe the condition know well the severe proportions which it may assume, the distress which it causes the patient, and the inadequacy of medicinal treatment or the usual dietetic restrictions.

The present communication forms part of a larger study on nephritis begun a number of years ago. Its purpose is to put on record certain facts concerning the nature of the anasarca occurring in chronic parenchymatous nephritis which are of clinical importance and to suggest a new method of treatment which promises to be useful. The reason for selecting this particular phase of the subject is the conviction (gained in the study) that the edema, or anasarca, is one of the most important phenomena in the disease, and that by its alleviation and prevention great progress is made toward ultimate relief of the renal condition.

Ever since Bright's discovery of renal disease the opinion has prevailed that all the phenomena associated with it are attributable to the pathological changes and the disordered function of the kidneys. It is now conceded that the morbid manifestations of chronic parenchymatous nephritis differ from all other forms of renal disease. Its onset, progress, and duration, its tendency to subcutaneous and serous effusions, and the cardiovascular conditions and urinary findings—all differ from those observed in other varieties of renal disease. It is not the object, at present, to discuss the chemical and pathological features of chronic parenchymatous nephritis as a whole, but it is important to note (and the conclusion seems justifiable from the observations thus far made) that among the cases of parenchymatous nephritis there is a group with a constitutional disorder in which the renal and other manifestations are concomitant or secondary in point of development and importance.

Much discussion has been indulged in concerning the origin of edema in nephritis, and many theories have been propounded concerning the mode of its production.

Thus it was[2] believed that the edema was the result of a "hydremia" from the retention of water caused by the inability of the kidneys to excrete it. Cohnheim[3] supposed that the edema was brought about by an increased permeability of the capillary vessels, induced by the malnutrition or poisoning incidental to the nephritis, which permitted fluid to filter through into the subcutaneous tissues and serous cavities. The hypothesis which has received the soundest clinical confirmation, and still retains many adherents, is that of Widal[4] and his associates, which teaches that the kidneys in this disease have a deficient capacity to eliminate salt (sodium chlorid). The accumulation of salt in

[2] v. Noorden: Pathol. d. Stoffw., 1906, i, 1043.

[3] Allg. Path., 1880, ii, 432.

[4] Bull. et mém. Soc. méd. d. hôp. de Paris, 12 Juin, 1902.

* Reprinted from *Am. J. M. Sc.*, 154: 638–647, 1917, with kind permission of the publishers.

This was the first explicit application of Starling's principle, stating the role of the plasma proteins in the distribution of body water, to the problem of edema formation in what is now known as the nephrotic syndrome. It has since been made clear that other factors also are important in this connection but even these are hinted at in Epstein's insistence upon the essentially extrarenal nature of "chronic parenchymatous nephritis," a position far in advance of his time.

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the body causes a retention of water, thus giving rise to the anasarca. Fischer's[5] view that the edema is due to an "acidosis" has not received confirmation.

These are the principal views concerning the production of effusions in the body in chronic parenchymatous nephritis. They all attribute the phenomenon in one way or another to the retention of water and salt caused by the inability of the kidneys to eliminate them adequately. The position of the kidney in the animal economy is such that alterations in renal function may result from causes outside the kidney, so that the retention of salt and water, with the consequent formation of edema, may be due to other factors than renal insufficiency. It is evident, of course, that no massive effusion could occur without a corresponding retention of fluid, but the cause need not reside in the kidneys.

Whereas it is undeniable that a state of hydremia of varying degree exists in chronic parenchymatous nephritis, just how such a condition can produce edema is not at all clear. In recent work Baehr and I[6] have found that in nephrectomized animals suffering from experimental diabetes a marked state of hydremia develops (increase of 70 per cent. in blood volume) without causing any edematous deposits. Concerning the view that increased permeability of the walls of the capillaries plays a part in the production of edema, it might be said that modern research indicates that the capillary vessels are less permeable to salt and water in renal disease than they are normally. Thus in the work of Chisholm,[7] Boycott and Douglas,[8] and more recently that of Bogert, Underhill and Mendel,[9] we find evidence that "the condition of nephritis produced experimentally 'effects an alteration in the permeability of the walls of the capillaries in such a way as to hinder the passage of fluid from the blood to the tissues.'" Widal's view that the retention of salt is directly and indirectly responsible for the production of edema would be valid on the basis of the evidence furnished were it not for the fact that numerous other affections of the kidneys also cause a retention of salt without ever leading to the development of edema. Other French observers[10] explain this discrepancy by assuming that the retained salt may exist in two states: one in firm combination with the tissue protoplasm—"chlorure fixé"—and the other, being free, "chlorure libre." The first phase gives rise to retention of salt without producing edema, "retention chlorure seche," the other phase leads directly to the retention of water, thus causing edema—"retention chlorure hydropigène." The explanation is ingenious but not convincing. Just why two such states for chloride retention should exist is not at all clear. One cannot deny Widal's observations on the effect of salt administration on the edema in chronic parenchymatous nephritis. That is as it should be. Neither can we gainsay the observation concerning hydremia and the retention of water. Least of all can we deny the fact that extreme forms of renal disease can exist, causing retention of different urinary substances without producing edema. Even total anuria of long duration may terminate and give no evidence of edema. Passler[11] records a case of anuria of eleven days' standing in which no edema developed.

It is evident, therefore, that more information is needed for the elucidation of this perplexing phenomenon. Some knowledge is gained by a comprehensive study of the blood sera and the effusions, particularly in the light of the newer physicochemical principles.

In 1912–1914[12] I published a series of papers recording the results of chemical studies upon blood sera and puncture fluids. The aim of these studies was to ascertain the various changes which the blood undergoes in different types of disease, particularly in respect to the proteins. Whereas no final deductions were drawn then from the variations encountered, certain points were definitely emphasized. It was observed that the proteins of the serum are subject to extensive variations. Whereas normally the blood serum contains 6 to 8 gms. of protein to the 100 c.c., of which a little more than one-third is globulin; in disease the quantity of protein may be very much reduced but the globulins may show both a relative and absolute increase. In the serum of cases of chronic parenchymatous nephritis the protein content

[5] Nephritis, 1912.

[6] Epstein, A. A., and Baehr, G.: Jour. Biol. Chem., 1916, xxiv, 1.

[7] Jour. Path. and Bacteriol., 1914, xix, 265.

[8] Ibid., 221.

[9] Am. Jour. Physiol., 1916, xli, 189.

[10] Marie, R.: Semaine méd., 1903, p. 385.

[11] Deutsch. Arch. f. klin. Med., 1906, lxxxvii, 569.

[12] Epstein, A. A.: Jour. Exper. Med., 1912, xvi, 719; 1913, xvii, 444; 1914, xx, 334.

shows the greatest reduction; whereas the increase in globulin content is most pronounced, and it may constitute nearly all of the protein present. (See Table I.)

For reasons which will be given in a future communication I am of the opinion that some of the changes occurring in the proteins of the serum, more especially the globulin content, are the result of well-defined influences acting upon the blood. In contrasting the findings in the sera of patients with different forms of renal disease the conclusion has been reached that chronic parenchymatous nephritis is genetically different from all other forms and that the change in the protein composition plays a direct part in the production of some of its clinical manifestations, particularly that of edema.[13] From a broad, clinical standpoint the cases of renal disease studied may be grouped into three classes.

1. The cases of chronic interstitial nephritis show no change from the normal in the character of the protein composition of the serum, nor in the ratio which the individual fractions bear to each other. On the other hand, the incoagulable and non-protein N of the serum show marked fluctuations, some of which correspond to the degree of functional deficiency of the kidneys.

2. In cases of localized disease of the kidneys (surgical conditions) the changes in the blood serum are twofold: One concerns the protein and is traceable to infections; the other concerns the non-protein constituents and varies with the amount of destruction of the kidney substance. When infection is present an increase in the globulins is observed similar to that occurring in infections in other localities; the non-protein N increases apparently in direct proportion to the degree of deficiency of the kidney.

3. In cases of chronic parenchymatous nephritis the amount of protein in the blood is markedly diminished. From the evidence which we possess the cause of the diminution of the amount of protein is ascribable largely if not entirely to the loss of protein in the urine. The amount of protein lost in the urine daily may be insignificant, and if immediately replaced may exert no influence on the content of the blood serum. As a rule, however, the loss is very considerable.

Dieballa and von Kétly[14] record a protein output in the urine of 24 gms. I have had occasion to observe an albuminuria of several months' duration, with a daily output of protein ranging from 18.5 to 26.2 gms. Now if we remember that the total protein in the blood averages only about 210 gms. the daily loss of so much protein eventually causes a tremendous drain upon the blood serum unless the deficit is replaced. Under normal conditions the loss of fluid from the blood (hemorrhage or otherwise) is immediately replaced by the passage of fluid from the tissue spaces back into the blood capillaries. The experiments of Turner, Marshall and Lamson[15] and their associates on plasmapharesis (*i.e.*, removal of plasma from the blood) show that the protein content of the serum gradually diminishes under such conditions.

In the nephritic individual the loss incurred may at first be covered so that no diminution in the blood-serum proteins may be evident; but as the disease progresses and the albuminuria becomes more intense the loss may exceed the amount restored, so that finally impoverishment of the serum in proteins results. As a rule the nutritional condition of the patients and the dietetic restrictions to which they are subjected in the course of treatment favor such a development.

The fact is that in chronic parenchymatous nephritis the quantity of protein in the serum is diminished. The decrease appears to be proportional to the intensity and duration of the disease. The reduction in the protein content of the serum is not due to the hydremia. The work of Dieballa and von Kétly[16] furnishes proof of that.

Neither is the diminution in the content of the

TABLE I.—AVERAGE COMPOSITION OF BLOOD SERA. GRAMS PER 100 C.C.

	Total protein.	Globulin.	Albumin.	Globulin per cent.
Normal	7.400	2.738	4.662	37.0
Cardiac conditions	6.408	2.240	4.417	33.9
Chronic interstitial nephritis	6.704	2.396	4.310	35.7
Chronic parenchymatous nephritis	3.928	3.462	0.466	89.2

[13] Ibid., 1914, xx, 334.

[14] Dieballa and v. Kétly: Deutsch. Arch. f. klin. Med., 1898, lxi, 761.

[15] Jour. Pharmacol., 1915, vii, 129.

[16] Loc. cit.

serum protein to be ascribed to a migration of the substance through the capillary walls into the tissue spaces. Chemical analysis of the edema fluids in the pure forms of chronic parenchymatous nephritis (by that I mean instances of the disease without cardiovascular involvement) shows that they are made up principally of salts and water.[17] The protein content is trifling. The conclusion is therefore unavoidable that the decrease in the protein content of the serum in these cases is to be attributed chiefly to the loss of protein in the urine. But what relation does this bear to the production of edema?

TABLE II.—AVERAGE COMPOSITION OF EFFUSION FLUIDS. SEROUS FLUIDS.

Cardiac conditions	3.352	1.199	1.788	43.0
Hepatic cirrhosis	3.174	1.318	1.856	41.0
Chronic parenchymatous nephritis	0.285	0.285	0	100.0
SUBCUTANEOUS FLUIDS.				
Chronic parenchymatous nephritis	0.098	0.080	0.018	81.0

In order to comprehend fully the nature of the processes which are active in the production of edema it is necessary to consider for a moment the manner in which the exchange of fluid between the blood and the tissues is regulated.

As stated before the loss of fluid from the blood is rapidly restored by the passage of fluid from the tissue spaces back into the blood capillaries. Two theories have been advanced to explain this absorption of fluid: (1) the backward filtration theory of Landerer, and (2) the osmotic theory of Starling. According to the first theory, when the pressure in the capillaries falls below that in the tissue spaces the fluid is forced back into the capillaries. When the reverse occurs, fluid passes from the capillaries to the tissue spaces. According to Starling there is normally a balance in the production and absorption of tissue fluid between the filtration pressure in the capillaries and the osmotic pressure of the colloids of the blood and tissue fluid.

Plasma and tissue fluid are practically identical in everything except protein. Starling[18] showed that the blood proteins exert an osmotic pressure of about 4 mms. of mercury for every 1 per cent. of protein. Normally the plasma contains more protein than the tissue fluid; so that normally an equilibrium is maintained in the to-and-fro movement of fluid by capillary pressure working from the vessels in the direction of the tissues and the osmotic pressure of the blood colloids acting in the reverse direction. Usually the osmotic pressure of the blood is greater than that of the tissue fluid because of the greater amount of colloids, and, as a result of this influence, the direction of flow is from the tissues to the blood capillary system. The effect of the two operating forces is naturally different. The one, capillary pressure or backward filtration (which is the active force in restoring blood volume after hemorrhage, etc.), must cause the passage of fluid which is approximately of the same composition as that contained at the source. For example if transudation occurs because of increased capillary pressure the migrating fluid must be like that of the blood serum. This is verified by the composition of effusions encountered in conditions of static disturbances, such as cardiac disturbances, cirrhosis of the liver, etc. (See Table II.) When the capillary pressure is lessened (as after hemorrhage) the composition of the fluid which passes from the tissues into the blood stream must be like that of the tissue fluid. Scott[19] in the study of this subject has shown that the fluid which passes from the tissues under these conditions contains from 0.6 to 2.09 per cent. of protein.

On the other hand, the fluid which passes in response to the osmotic pressure of colloids should be practically a solution of salts. Analysis of the edema fluid encountered in cases of chronic parenchymatous nephritis shows the composition to be one of salts and water. (See Table II.) The protein content is insignificant and may be derived from the fluid of the tissue spaces.

We have in these considerations a set of facts which dovetail and afford us a starting-point for the comprehension of the mechanism which leads to the production of edema. It is recognized on the one hand that the blood serum normally contains more protein, *i.e.*, more colloid material than the tissue fluid, and that by virtue of this predominance it possesses a greater osmotic pressure which is vital in maintaining a balance in the exchange of fluid

[17] Epstein, A. A.: Jour. Exper. Med., 1914, xx, 334.

[18] Quoted from F. H. Scott, Jour. Physiol., 1916, 1, 157.

[19] Jour. Physiol., 1916, 1, 157.

between the blood and the tissues. The examination of the blood sera in cases of chronic parenchymatous nephritis reveals the fact that the protein, *i.e.*, the colloid content, is very much reduced, a loss sometimes equivalent to 60 or 70 per cent. and more of the total serum protein. In terms of osmosis this loss of protein represents a pressure equal to 20 to 24 mms. of mercury, a factor sufficient to disturb the equilibrium in the exchange of fluid between the blood and the tissues. More precisely the deficit in serum protein causes a fall in the osmotic pressure of the blood. This disturbance does not only favor the passage of fluid from the blood to the tissues, but also gives to the tissues the controlling power to absorb and retain fluid.

From the very nature of the force which is concerned in the process (namely, that of osmosis) the fluid which passes from the blood to the tissues must be a solution of salts. The fluids which we find in the effusions in chronic parenchymatous nephritis are practically such solutions. (See Table II.) As pointed out before, the protein content is negligible and may not be derived from the blood.

The hypothesis for the production of edema in chronic parenchymatous nephritis which I therefore propose is briefly as follows: The loss of protein incurred by the blood serum through the continuous albuminuria causes a decrease in the osmotic pressure of the blood, which fact favors the absorption or imbibition and retention of fluid by the tissues. This conclusion gains support from the experiments performed by Tullio Gayda,[20] who found that the edema which is produced in perfusion experiments when normal saline or Ringer solution is used is prevented by the addition to the perfusing fluid of colloids which are in osmotic equilibrium with the colloids of the lymph and tissues. This may not be the only factor but it is an important one.[21]

Other evidence is also available to confirm this view, but space will not permit of elaborating further upon this phase of the subject. Suffice it to say that through a change in the protein composition of the blood plasma a condition is produced which is capable of causing the retention of fluid in the tissues.

TABLE III.—CHOLESTERIN CONTENT OF BLOOD SERA. MILLIGRAMS PER 100 C.C.

Diagnosis.	Cases.	Average.	High.	Low.
Chronic interstitial nephritis	24	174	265	100
Uremia	5	133	194	87
Arteriosclerosis	7	163	218	100
Cardiac conditions	19	157	294	104
Bichloride poisoning	2	127	130	125
Chronic parenchymatous nephritis	9	559	1230	333

Certain other factors which are important in the chemical and physical pathology of the disease must be touched upon, as they enter largely into a consideration of the treatment. Whether it be that a state of malnutrition results from the impoverishment of the blood in proteins or that the diseased condition, commonly termed chronic parenchymatous nephritis, is genetically a disorder of nutrition, we find in the blood definite evidence of tissue starvation. The evidence which I have in mind is the remarkable increase in the lipoid content of the blood. A number of such observations are on record. Thus Chaufford, Rechit and Grigaut[22] have noted an increase in the lipoid content. Recently I had occasion to observe very unusual amounts of lipoid substances in the blood serum of cases of parenchymatous nephritis. (See Table III.) The accumulation of these substances in the blood probably arises partly from the mobilization of fat deposits from the subcutaneous tissues and other sources and to a large extent perhaps from degenerative processes in the tissues. The cause of fat mobilization when a lipemia develops may be partly physical displacement, due to the effusions. Usually, however, the condition in the blood is one of lipoidemia, thus pointing to a metabolic derangement similar to that observed in starvation in advanced diabetes and in pellagra. The degree of nutritional disturbance and fat mobilization can be appreciated only after the cases begin to improve and the edema subsides. Then the patients manifest very marked wasting.

The increase in the lipoid content of the blood is important not only because it gives evidence

[20] Arch. Sc. Med., 1916, xxxix, 389.

[21] The increase in the globulin content of the blood serum, and the excessive accumulation of lipoids, constitute additional factors which contribute to the causation of edema in chronic parenchymatous nephritis, and interfere with the elimination of salt and water by the kidneys.

[22] Compt. rend. Soc. de biol., 1911, p. 317.

of a grave nutritional disturbance but also because it affects the pathology of the disease in other ways. Kaethe Dewey has[23] recently shown that the mere presence of excessive amounts of cholesterin in the blood is capable of producing definite pathological lesions in the kidneys and perhaps also affecting their function. From the work of Mathilde Koch and Carl Voegtlin[24] and also that of Herlizka[25] and Gayda[26] it appears that abstractions of lipoids from tissue cells cause imbibition of fluid with consequent swelling of the cells.

The problem in the treatment of edema in chronic parenchymatous nephritis is to relieve the condition and prevent its recurrence. The mere removal of effusion fluid by paracentesis and puncture, if feasible, may relieve it partly, but does not, as a rule, prevent a reaccumulation. I need not dwell upon the medicinal means used to promote renal activity. The failure of such procedures to influence the edema is classic. It has been shown repeatedly that the kidneys in this type of disease are capable of eliminating the different urinary substances. Their inability to excrete sufficient salt and water is due to causes outside of them.

On the basis of the views presented concerning the causation of edema the real problem in its treatment is the restoration of normal conditions in the blood and the establishment of a healthy state of nutrition. The blood in these cases, as previously stated, shows a marked decrease in protein and an increase in lipoids. The indications are: (1) to increase the protein content of the blood and thus help it regain its normal osmotic power, and (2) to remove or cause the reabsorption by the tissues of the excessive lipoids. The restoration of the protein content may be accomplished by two methods: (1) Massive infusion or transfusion of healthy blood accompanied by the removal of equal quantities of blood from the patient. The latter procedure is necessary to accommodate the introduction of additional blood so as not to embarrass the circulation. It also serves to remove some of the excessive lipoids. (2) Most important is the proper administration of a high protein and fat-poor diet.

The employment of transfusion is undoubtedly helpful and affords a good start in the treatment, but, of course, is not always feasible for obvious reasons. It must be remembered also that whereas the replacement of the impoverished blood of the patient with healthy blood helps toward the restoration of normal conditions, the effect is necessarily only a temporary one, for the continuation of the albuminuria causes a constant loss of blood protein. Chief reliance must therefore be placed upon adequate dietetic measures. The method consists, therefore, in the administration of large quantities of properly selected proteins with a minimum of carbohydrates and the exclusion of fats. The reason for restricting the carbohydrates is twofold: (1) to promote a maximum assimilation of protein, and (2) to exclude the greater production and retention of water which is incidental in the metabolism of carbohydrates. The fats are excluded because of the marked increase of fatty substances in the blood.

DIET EMPLOYED.

	Daily amount
Food value	1280 to 2500 calories
Proteins	120 to 240 grams
Fats (unavoidable)	20 to 40 "
Carbohydrates	150 to 300 "

ARTICLES USED.

Lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea and cocoa.

As for the administration of fluids and salts, I might say that the fluid allowed is restricted to the quantity present in the food, plus that which is necessary for the comfort of the individual patient, amounting usually to 1200 to 1500 c.c. The amount of salt allowed is the quantity sufficient to make the food palatable.

The method is necessarily slow and requires persistence, but its effect is indeed very salutary. The protein content of the blood increases and the lipoidemia subsides. Accompanying these changes in the blood there is a progressive increase in the excretion of urine with a gradual disappearance of the edema. The albuminuria also diminishes and the patient's health improves steadily.

The diet listed above is relatively low in calories; other articles of food are added gradually as conditions allow. The fats are restricted so long as the lipoid content in the blood remains elevated.

The number of cases treated thus far is not large, but such of them as we had represented extreme types of the disease. The results obtained have been very encouraging. A detailed report of these cases will be published later.

[23] Arch. Int. Med., 1916, xvii, 757.
[24] Bull. Hyg. Lab., 1916, No. 103. p. 129.
[25] Arch. di Fisiol., 1909, vi, 369.
[26] Loc. cit.

The Nonoperative Determination of Patency of Fallopian Tubes*

By Means of Intra-uterine Inflation with Oxygen and the Production of an Artificial Pneumoperitoneum

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THE determination of patency of fallopian tubes has hitherto been possible only by direct inspection and palpation obtained by laparotomy. Physical examination was wholly inadequate because it still left the question of patency a matter of speculation. This is especially true when, as in certain instances, the tubes are sealed tight at their fimbriated end, although no distention of the lumen is present. In other instances it is hard to diagnose occlusion of the tube due to hydrosalpinx when the walls are flaccid. Some tubes are closed by adhesions secondary to a peritonitis that arises outside of the gynecologic domain. No matter how clear the history, the question as to whether such a tube is patent or not is always a matter of doubt. The same holds true in cases in which the tube may be occluded by a tumor.

An accurate knowledge of the anatomic patency of the tubes is admittedly important in formulating prognosis and therapy of female sterility. If we are aware that a patient is sterile because her fallopian tubes are closed, plastic operations on the cervix, curettage, dilatation and opotherapy will obviously be useless.

It is well to remember, as Giles states, that practically 11 per cent. of female sterilities is due to tubal disease. In women under 24 years of age it is higher, reaching 14.4 per cent. Add to these 4.4 per cent. of cases due to blocking of the fallopian tubes by peritonitis, and we have an average incidence of 15 per cent. of cases of sterility due to pathologic tubes. For convenience we will not include tumor formations and malformations. It will then be seen that one out of six or seven women owes her sterility to closed tubes.

Here it may be mentioned that, in certain cases in which no gross physical abnormality can be elicited by examining the woman (2 per cent. of cases) and the potency of the male partner is established by the finding of live spermatozoa in the cervix and fundus uteri, a congenital atresia of the tubes or of some part of the lumen may be the real cause of the sterility. One naturally hesitates to subject such a woman to an exploratory laparotomy, so that a method whereby patency of the tube could be demonstrated without surgical means is eminently desirable.

INTRA-UTERINE OXYGEN INFLATION AS A METHOD OF DIAGNOSIS

This I believe has been effected by the combination of oxygen with fluoroscopy and roentgenography. It is possible to determine whether the tubes are patent or otherwise by inflating the uterus with oxygen and in normal cases filling the peritoneal cavity with a measured quantity of oxygen. The artificial pneumoperitoneum establishes definitely the patency of the fallopian tubes. In a preliminary report I pointed out that the peritoneum tolerates the oxygen introduced by way of the uterus and fallopian tubes equally as well as by direct abdominal puncture. There is no doubt, however,

* Reprinted from *J. A. M. A.*, 75: 661–666, 1920, with permission of the publishers. To conserve space it has been necessary to delete a considerable part of the text, together with figures and one table.

The details of the method introduced by Dr. Rubin have since been improved but the principle remains standard procedure for determining the patency of the fallopian tubes. A. B. G.

that the result is the same whether the peritoneum is filled with oxygen through the abdominal wall by puncture or through the uterine cavity without puncture. For general abdominal diagnosis at least a liter to a liter and a half of gas is necessary. For the specific purpose of establishing the fact of open fallopian tubes the amount of oxygen need not exceed 300 c.c., and in the last of my cases tested by this method about 150 c.c. would be the average volume used.

In the first patient in whom I injected oxygen through the uterus I did not measure the quantity but allowed it to pass into the peritoneal cavity till a moderate amount of visible distention resulted. The fluoroscopic and roentgenographic pictures were the same as described by Stein and Stewart, who introduce the oxygen through a trocar or needle thrust into the abdominal wall.

In the next thirty-two cases of sterility examined by intra-uterine oxygen inflation it was endeavored to establish several points: (1) the tolerance of the patient for the method as a diagnostic procedure; (2) the possible danger of infection; (3) the danger of embolism; (4) the diagnostic reliability of the findings and interpretation, and (5) the minimum volume of oxygen necessary to produce the pneumoperitoneum which could be seen by fluoroscopic examination.

1. *Tolerance of the Patient.*—The patients stood the examination with very slight discomfort. The passing of the oxygen into the peritoneal cavity is painless. Uniformly there is some sense of pressure about the diaphragm within five or ten minutes, and slight "sticking" sensations in one or both shoulders. A half liter of oxygen causes very moderate symptoms. A liter of oxygen is followed by greater epigastric oppression and shoulder pains. When more than a liter is used, the symptoms are proportionately increased. When from 100 to 200 c.c. are injected, the symptoms are very slight and do not interfere with the patient's daily routine.

2. *Possible Dangers of Peritoneal Infection.*—There are no pelvic symptoms after the gas inflation. In no case was there evidence suggestive of peritoneal irritation. There was no nausea or vomiting, pains, rigidity or tenderness, or rise in temperature or pulse rate.

3. *Possible Dangers of Embolism.*—In no instance were there symptoms suggestive of air embolism. This question gave me some concern in first contemplating the method. By actual experiment on the dog I found that the animal tolerated 350 c.c. of oxygen introduced directly into the leg vein without any symptoms attending the injection or following it. The rate of oxygen flow was the same as employed in my sterility patients. As 350 c.c. is the very maximum amount required, I felt that the accident of embolism from oxgen could be disregarded. I have since learned that a number of army surgeons use this method of intravenous oxygen injection for therapeutic purposes, especially in pneumonia.

4. *Diagnostic Reliability of the Findings and Interpretation.*—When an artificial pneumoperitoneum was produced, it was conclusive in proving the patency of the genital canal from the external end to the internal abdominal end. This, however, could result when only one tube was patent and the other closed, as well as when both tubes were actually patent. For practical purposes in the consideration of sterility it suffices that one fallopian tube is patent. Future observations may make it possible for us to draw definite conclusions on the question of unilateral or bilateral patency, and, if unilateral, which side is open or closed. At this time I am not prepared to present data on this point.

When an artificial pneumoperitoneum does not result from the intra-uterine oxygen inflation, the probability is that there is some obstruction in the genital canal above the internal os. It may be at the uterine ostium of the fallopian tubes, along their course, or at the fimbriated end. Whether this be by uterine cornual polypi occluding the opening as a ball valve or inspissated mucus in the tubal lumen, or agglutination of the plicae of the endosalpinx or a sealing over of the fimbria, the result will be the same. One negative result is not enough to establish nonpatency. In such an instance the test is repeated once or twice, a little more gas being used each time. If in the repeated tests the oxygen fails to pass through, we may conclude that the patient is sterile because of this mechanical blockade. Occasionally, however, when the stenosis operates like a ball valve, as in the case of a polyp at either uterine horn, the greater pressure by the increased gas volume may succeed in forcing the oxygen through, and then a pneumoperitoneum would result. In such an event, however, the test would still have a certain diagnostic value and might serve to indicate the proper therapeutic measure to be adopted to overcome this difficulty. Inspissated mucus at

the uterine end of the tube would have the same effect, and here, too, the negative result is significant of a mechanical cause of sterility.

These results I was able to demonstrate on the extirpated uterus with adnexa attached.

As far as introducing infective material from the uterine cavity into normal tubes and thence into the peritoneum is concerned, several factors make that highly improbable. One is that the cavity of the body of the uterus is in most cases free of infection. Pus or mucus, if present, is more likely to descend from infected tubes. When the uterine discharge is frankly purulent, the method is not to be used. Against this theoretical objection is the practical fact that in none of the seventy cases has there been such an occurrence.

In the nonpatent cases one may also use thorium or bromid as a control. The citrate thorium solution or sodium bromid solution may be injected into the uterus, and under obturation the roentgenogram may be made. I did this a few times in the earlier experiments, but have been able to dispense with it in my later work.

TECHNIC

The technic of the procedure is very simple. The instruments needed for the intra-uterine injection are (1) a metal cannula (Keyes-Ultzman type) perforated at the tip by several small apertures; (2) a tenaculum (bullet) forceps; (3) a uterine sound; (4) a dressing forceps; (5) a bivalve vaginal speculum (Graves type), and (6) an oxygen tank connected with a water bottle. The rubber stopper is perforated at three points through which bent glass connecting tubes pass into the bottle; one of these glass tubes connected with the oxygen tank tips down below the water level. The two other glass tubes dip down for 1 or 2 inches, and do not reach the water level. One of these is attached by rubber tubing to a mercurial manometer and the other is attached in the same way to the metal cannula. In order to determine the volume of oxygen gas released from the tank, it is allowed to pass through the water bottle in a stream of discrete bubbles. These should not exceed 300 per minute. The actual amount per minute can then be measured by displacing an equivalent quantity of water from a graduated bottle into another.

The cervix is exposed by means of the speculum; the vagina is carefully wiped clean and the cervix is cleansed dry and painted with tincture of iodin. If there is any uncertainty regarding the direction of the uterine cavity, it may be determined by passing the sound. The cervix is steadied with tenaculum forceps grasping its anterior lip. The oxygen, which has been released from the tank and regulated, is now allowed to pass from the water bottle through the glass and rubber connecting tubing to which the metal cannula is attached. By pinching the rubber tubing near the cannula one can make sure that all the joints are air tight. The mercury immediately rises in this case. If there is some leakage between the oxygen source and the cannula, the pressure will be negative. This is a very important point to be observed. Having made certain of the pressure, the air valves in the manometer are opened and the catheter is then inserted into the uterine cavity to a point well beyond the internal os. This is done so that there is no immediate escape back along the cervical canal and out into the vagina. The rubber urethral tip, placed ordinarily from 1½ to 2 inches away from the cannula tip, is then fitted into the external os, insuring better obturation. This is not essential in the nulliparous intact cervix, but is required in the irregular patulous external os resulting from previous operations or from lacerations attending childbirth. The air valves are now closed. Within a few seconds after the oxygen enters the uterine cavity, the pressure as noted in the mercury manometer will rise; within from one half to three quarters of a minute in the patent cases the mercury reaches its maximum point. It then fluctuates for a few seconds or drops rather sharply from 10 to 30 points, maintaining the last level more or less for the rest of the time. There may be a slight audible escape of oxygen from the external os in the cases of patent tubes, but as a rule there is none till the cannula is removed, when slight regurgitation is present.

In the nonpatent cases, the pressure usually rises steadily for three quarters of a minute to a minute or longer, and then drops sharply as the gas regurgitates into the vagina. As the time required for sufficient oxygen to pass into the abdomen where it can be detected by fluoroscopic examination is one and a half minutes, the cannula is not withdrawn till this time limit is reached. If the pressure reaches 200 mm. in one minute, it is well to open one of the air valves (needle valve) to prevent it from mounting higher. In all our patent cases this high level was not reached.

The intra-uterine gas pressure has been a valuable adjunct in checking up the time required for the gas to pass through the tubes and reach the peritoneal cavity. With the manometer attached to the water bottle we can decide, knowing the rate of flow beforehand, how much we wish to inject into the abdomen. From the moment the pressure falls, we allow the gas to flow for from one-half to one minute, and can estimate the quantity used with reasonable accuracy, allowing for an error of 50 c.c., which for practical purposes is unimportant.

Various types of pressure devices were tried to estimate intra-uterine gas pressure. The mercury manometer of the standard type was finally adopted. For this advice I am indebted to Dr. Arthur J. Bendick, associate roentgenologist to Mount Sinai Hospital.

In the positive patent cases, the pressure need not exceed 40 mm. The average pressure is from 60 to 80; occasionally the pressure rises to 100 or more before the oxygen will pass through the uterine ostium of the fallopian tubes. When the pressure reaches 150 or more, the likelihood is that the tube lumen is closed completely or stenosed, but not necessarily in every case. A pressure of 200 is tolerably certain to be due to closed tubes.

While the pressure gage as studied in the second series of thirty-seven cases is an excellent indication of patency of the fallopian tubes, it is well always to examine the patient with the fluoroscope. It occasionally happens that with the greater pressure a slight amount of gas succeeds in entering the peritoneal cavity and reaching the subphrenic space on the right or left side, where it can be detected by the roentgen ray.

In the positive cases, that is, when the tubes are patent, the oxygen will be seen as a clear space below the diaphragm, most often on both sides, but occasionally on one side only. The space varies, depending on the volume of oxygen injected. In the average case in which from 150 to 250 c.c. is used, this clear space below the diaphragm varies between one-quarter to 1 inch in depth. The diaphragm appears as a transverse septum above the dense liver shadow on the right side and over the pale stomach margin on the left. It is unmistakable, and is readily seen when the patient breathes deeply. In all our cases in which we have made roentgenograms the finding was always confirmatory.

The whole examination is complete within five minutes. When the minimum volume of oxygen has been used, that is, from 100 to 150 c.c., the symptoms are negligible. There is the slightest discomfort around the diaphragm, and slight sticking pains referred to one or both shoulders. The patient dresses herself and is able to go home with comfort. When, however, more gas has been used, the symptoms may be somewhat annoying. In such cases it is well for the patient to lie down for a few hours on reaching home, with the foot of the bed elevated (moderate Trendelenburg posture).

In the negative cases, that is, when the tubes are occluded, no artificial pneumoperitoneum results. These patients have no discomfort after examination, and have none of the referred pains in the shoulders or about the diaphragm.

In none of the cases are there pains in the pelvis following the intra-uterine oxygen injection. A little bloody oozing for a few minutes follows a withdrawal of the cannula, particularly in cases just before or just after the menstrual period. It is well, therefore, to make the examination about ten days after the menstrual period.

RESULTS OF EXAMINATION

Altogether seventy cases were examined by the method of intra-uterine oxygen inflation; thirty-three without the control of the manometer, and thirty-seven with the manometer. In the first group various quantities of gas were used to establish particularly the minimum amount required to produce an artificial pneumoperitoneum without, however, the annoying symptoms which would destroy the usefulness of the method as a diagnostic aid. Various types of sterility cases were tested. Some were primary sterilities, the marriage dating back from one to twelve years or more and in which no operations were performed either to relieve the condition or for tubal, ovarian or uterine disease. Some of the patients had had one or several curettages for the relief of sterility; some for alleged miscarriages. A few had had one child and became relatively sterile for a number of years. A few cases in which it was definitely known that one or both tubes were ablated on account of pyosalpinx were used as controls to check up the diagnostic value of the method. A few patients had had plastic operations on the cervix for the cure of primary sterility.

INDICATIONS FOR THE APPLICATION OF THE METHOD

The method is indicated:

1. In all cases of primary sterility in which all factors except that of tubal disease may be excluded. Here it has a definite prognostic as well as diagnostic value.
2. In cases of primary sterility in which the patient is known to have passed through a pelvic infection of gonorrheal origin.
3. In cases of primary sterility in which the patient had peritonitis of appendicular origin.
4. In cases of relative sterility in which the patient had a pelvic infection following childbirth or abortion, particularly when induced.
5. In cases of one child, sterility without the definite history of pelvic infection.
6. In cases in which it had been necessary to remove one whole tube and part of another for hydrosalpinx or pyosalpinx (conservative surgery).
7. After unilateral ectopic pregnancy to determine the patency of the residual tube.
8. After cases of salpingostomy for the cure of sterility of tubal origin to demonstrate the success of the operation which was calculated to effect open tubes.
9. After sterilization by tube ligation to test the patency of the tied or severed tubes.
10. After multiple myomectomy to make certain that at least the uterine ostium of the tube has been left intact.

CONTRAINDICATIONS

The method is not to be used in the presence of any acute subacute pelvic infection, nor in the presence of purulent diseased bartholinian glands, urethra, vagina or cervix.

The causes of sterility are too often obscure and undetermined. It appears, however, that at least the mechanical factor of patency should be possible of determination in most cases. The method of intrauterine oxygen inflation with the production of an artificial pneumoperitoneum obviates the necessity of surgical exploration and is especially serviceable in the obscure cases.

An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries*

An Undescribed Disease

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THIS case is remarkable, clinically and anatomically.

REPORT OF CASE

History.—K. Z., a girl, aged 16 years, was an elementary school graduate, had gone to business school, and had been employed for eight months preceding the illness. There were three other children, two younger and one older; all apparently were perfectly normal. There were no home difficulties, and poverty was not extreme. She had spent September 4 and 5 at Rockaway Beach, where she appeared in perfect health and spirits. She had returned home on the evening of September 5 and slept well. On the morning of September 6, she complained of weakness in the upper extremities and had pain on moving the wrists and elbows; she already had marked pallor and was slightly constipated. The symptoms increased in severity until she was admitted to the Beth Israel Hospital, September 15. While at home, she had a constant fever, the temperature rising once to 104 F. and staying at other times between 101 and 102 F.

Physical Examination.—The patient was a pale girl with "café au lait" tinge. A few petechiae were present on the left arm. The lungs and heart revealed nothing abnormal. The spleen and liver were not enlarged. The abdomen was lax and not tender. September 18, the red blood count was 1,330,000; the hemoglobin, 40 per cent.; the leukocytes, 12,600, of which 65 per cent. were polymorphonuclears. The red cells revealed a central pallor, but there were no nucleated elements. A fragility test showed hemolysis to begin at 0.8, and to be complete at 0.19 (?). No platelet count was made. September 19, the red blood count was 1,120,000; the hemoglobin was 40 per cent., and the leukocytes were 19,000. A blood culture remained sterile.

The urine showed marked traces of albumin with hyaline and granular casts.

The blood chemistry, September 16, showed: urea, 21.2 mg. per hundred cubic centimeters; nonprotein nitrogen, 31.25 mg. per hundred cubic centimeters, and creatinin, 1.1 mg. per hundred cubic centimeters. The feces and gastric contents gave a marked reaction for occult blood.

Roentgen-ray examination of the chest showed nothing abnormal. The electrocardiogram showed inversion of the T wave in Lead III. The temperature, on admission, was 101.8 F. During the week the patient was in the hospital, it ranged between 100 and 102 F. The pulse varied between 100 and 130. The respiration was around 20. The systolic blood pressure was 130, and the diastolic, 60.

September 19, there was partial paresis of the

* Reprinted from *Arch. Int. Med.*, 36: 89–93, 1925, with permission of the publishers. The illustrations of hyaline thrombi in various organs have been omitted.

At the time this report was written Dr. Moschcowitz was serving as pathologist to the Beth Israel Hospital, where the patient described died, as well as on the medical staff of The Mount Sinai Hospital. The case is generally accepted as the first recognized instance of the still obscure disease now known as thrombotic thrombocytopenic purpura, thrombocytic acroangiothrombosis or generalized platelet thrombosis. A more complete description of the entity was given later by Baehr, Klemperer and Schifrin (An acute febrile anemia and thrombocytopenic purpura with diffuse platelet thromboses of capillaries and arterioles, *Tr. A. Am. Physicians*, 51: 43, 1936). A. B. G.

left arm and leg; also, a slight facial paralysis. The following day, a double Kernig reflex was noted. That night there was pulmonary edema, which responded to treatment. Soon after, the patient went into coma; respirations became irregular, and she died, September 20. Dr. E. Libman, who saw this patient in consultation, recognized the condition as a new disease.

Necropsy.—A partial necropsy was done. The body was pale and poorly nourished. The lower lobes of both lungs showed marked congestion. The heart was slightly enlarged; the left ventricle was hypertrophied; the muscle was firm and pale. The mitral and aortic valves were normal. The liver was slightly enlarged, pale and fatty; there was slight nutmeg change. The spleen measured 11 by 8 by 3 cm., and weighed 165 gm. The surface was smooth. On section, the organ was deep mahogany red, somewhat soft and velvety. The malpighian bodies were prominent. The kidneys were large; the capsules were smooth and not adherent; on section, the organ was deep red.

The anatomical diagnosis was anemia; acute congestion at the bases of both lungs; hypertrophy of the left ventricle of the heart; hyperplasia of the spleen, and congestion of the liver and the kidneys.

Microscopic Examination.—The lungs were edematous; at the bases, there was congestion of the parenchyma. The heart muscle revealed a striking appearance. With the low power of the microscope, practically every field revealed from one to a dozen structures that were unquestionably thrombi in the terminal arterioles or capillaries. These varied in appearance and revealed progressive changes depending on the amount of organization that had taken place. The earliest (Fig. 1) showed merely a plugging of the vessel with a hyaline mass which either partially or completely filled the lumen. Usually, even in this stage, the plug, if not in intimate contact with the wall of the vessel, was surrounded by a layer of flat cells of the fibroblastic type which was distinct from the endothelial intima. In older plugs (Figs. 2 and 3), fibroblasts penetrated into the hyaline mass, and the older the plug, the greater became the amount of fibroblastic infiltration at the expense of the hyaline material; eventually, a small fibroblastic tubercle-like structure was formed. In some of these thrombi, the origin of these fibroblasts from the endothelium of the vessel was plainly discernible. At the same time, the process of organization within the lumen was accompanied by a fibroblastic process around the wall of the vessel in concentric fashion; with the van Gieson stain, some gave the reaction for fibrous tissue. Karyokinetic figures in these fibroblasts were common. In some vessels in which the plug had not completely filled the lumen, tiny spaces were formed in which fresh red cells were visible. Only the terminal arterioles and capillaries were involved. The larger vessels with well defined muscular walls showed no change whatever, either in the form of thrombosis or changes in the intima. Every section of heart muscle was involved, the ventricles, the auricles, the papillary muscles and the septum; they were even visible in some of the vessels of the precordial fat. In addition, there was moderate edema of the parenchyma. The liver showed a moderate fatty infiltration and slight congestion around the central veins. Very few hyaline thrombi in the early stages were noted. The spleen showed enormous congestion of the sinuses. A few hyaline thrombi were present in some of the central vessels of the malpighian bodies. The kidneys showed marked parenchymatous degeneration in the tubules and congestion of the parenchyma. The malpighian tufts were clear. Many of the arterioles and capillaries in the middle zone, in the region of the vasa recta, showed hyaline thrombi of the same morphology as those in the heart (Fig. 4). No bacteria, tubercle bacilli or spironema pallida were found in any of the tissues.

A fairly complete search of the medical literature fails to reveal a case resembling this, either clinically or anatomically. Hyaline thrombi have long been recognized but never in respect to the enormous spread and distribution revealed in this case. Klebs[1] apparently was the first to describe these thrombi; he noted them in cases of extensive burns. They have been described in a wide variety of conditions. Thus, Kaufman[2] found capillary red cell thrombi in cases of mercury poisoning. Schmorl[3] found them in the stomach and liver after abrin poisoning. Flexner[4] noted such thrombi in the neighborhood of ulcerated typhoid ulcers of the ileum and in the lung, associated with bronchiectasis; also in the liver in eclampsia, and in

1. Klebs: Handb. d. path. Anat. Berlin, 2:114, 1868–1880.
2. Kaufman, quoted by Dietreich (Footnote 6).
3. Schmorl: Jahresb. d. Gesellsch. f. Nat.-u. Heilk. in Dresd., 1899–1900, quoted by Flexner (Footnote 4).
4. Flexner: J. M. Res. 8:316, 1902.

the stomach after carbolic acid poisoning. He also states that they have been found in pneumonia, diphtheria and in some of the acute infectious diseases. Loeb, Stricker and Tuttle[5] noted red cell thrombi in the lungs of animals after the injection of a foreign serum. Dietreich[6] found such thrombi in animals after the injection of an extract from beans. Bacterial infections are common causes of such thrombi, for they have been produced experimentally, in infections, by the hog cholera bacillus (Boxmeyer[7]), the pneumococcus and the staphylococcus aureus.

The true pathogenesis of hyaline thrombi was not known until Flexner showed that they arose from agglutinated red cells. This he proved by injecting the highly agglutinative substance, ricin, into rabbits. He concludes that when red cell thrombi are old or when agglutination is compact, they have the appearance of hyaline thrombi. He also states that poisons that destroy red blood corpuscles rapidly provoke agglutinative thrombi, and that the so-called fibrin ferment thrombi are probably agglutinative thrombi. Pearce,[8] indeed, obtained hyaline thrombi in the liver associated with focal necroses by injecting agglutinating serums. He also injected filtered autolyzed products of various bacteria which possess hemagglutinins of low activity and obtained similar necroses of the liver associated with fused red blood cell thrombi, i. e., structures resembling hyaline thrombi.

In this condition, it is interesting to note that, as far back as 1875, Landois[9] found that an injection of foreign blood causes multiple capillary thrombosis.

I have learned that Dr. Max Lederer of Brooklyn has seen four cases clinically identical with the one described in this report. He permits me to state that, thus far, no cause has been found, and that all four patients recovered promptly after a single transfusion of blood.

From these observations we conclude that death, in the case described, resulted from some powerful poison which had both agglutinative and hemolytic properties. If opportunity offers, further investigation will be made of this strange disease with strange pathologic morphology.

5. Loeb, Stricker and Tuttle: Virchows Arch. f. path. Anat. **201**:5, 1910.
6. Dietreich: Centralbl. f. Path. **23**:372, 1912.
7. Boxmeyer: J. M. Res. **9**:146, 1903.
8. Pearce and Winne: Am. J. M. Sc. **128**:669, 1904.
9. Landois: Die Transfusion des Blutes, Leipzig, 1875, p. 225.

Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen*

A Hitherto Undescribed Type

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THE clinical picture of a general adenopathy associated with enlargement of the spleen is encountered in a variety of disease conditions. The chronic diseases in adult life in which this association of symptoms is dominant are the leukemias, the infectious granulomas (under which are included Hodgkin's disease, syphilis and tuberculosis) and lymphosarcomatosis. However, in the last ten years we have accumulated three instances of a general adenopathy with splenomegaly which do not represent any of the groups just mentioned, and furnish examples of a condition which we believe has escaped recognition or at least, if seen, has not been reported or recorded as a disease entity. We base this statement on the fact that a diligent and conscientious search of the literature has failed to reveal more than one instance identical with, or even similar to, the group that is presented here. This case was reported by Becker[1] in 1901. A lymph node was removed during life, three years after onset of the disease, and considered as hyperplastic by the pathologist. The adenopathy and splenomegaly subsided somewhat after arsenic medication. We have assumed the responsibility of naming this condition splenomegalia lymphatica hyperplastica.

Localized hyperplasia of lymph nodes of long standing (so-called lymphomas) has been reported by LeCount,[2] Ewing[3] and others. A similar lymphoid hyperplasia involving only the spleen (splenic lymph-adenosis) was noted by Josselin de Jong[4]; splenectomy proved successful in this condition. Hitzrot also removed a similar spleen.[5]

The first case was brought to our attention by the examination of a lymph node and spleen removed by Dr. Howard Lilienthal in 1914. The patient, a woman, died following the splenectomy, and no necropsy could be obtained. The clinical notes speak of a general adenopathy with a very large spleen and a negative blood picture. The surgeon removed the spleen on account of the physical discomfort that it caused the patient. On examination, the enormous spleen showed a giant hyperplasia of the malpighian bodies, such as will later be described in detail. This striking pathologic picture was recalled by one of us when two other patients appeared last year at about the same time in the service of the First Medical Division of Mount Sinai Hospital. These two patients were women, aged 28 and 32, respectively. Each had noticed swellings on both sides of the neck and gradually increasing size of the abdomen accom-

1. Becker, E.: Deutsch. med. Wchnschr. 27: 726, 1917.

2. LeCount, E. R.: J. Exper. Med. 4: 559, 1899.

3. Ewing, J.: Neoplastic Diseases, Philadelphia, 1919, p. 336.

4. Josselin de Jong, R.: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's) 69: 185, 1921.

5. Hitzrot, cited by Pool, E. H., and Stillman, R. G.: Surgery of the Spleen, New York, 1923.

* Reprinted from *J. A. M. A.*, 84: 668–671, 1925, with the kind permission of the publishers. The reprint is complete except for omission of one photomicrograph of a typical lymph node under low power.

This report gives a clear and concise account of a new entity now well established. Subsequent experience has shown, however, that the course of the disease ultimately is more malignant than here indicated and, to conform with this, the designation has been changed to giant follicular lymphoblastoma. (BAEHR, G. and KLEMPERER, P. *New York State J. Med.*, 40: 7, 1940.) A. B. G.

panied by marked discomfort and at times pain on the left side. A splenectomy was done in one instance on account of progressive anemia and evidence of marked blood destruction. Later we learned that better results can be accomplished with radiotherapy.

REPORT OF CASES

CASE 1.—S. B., a woman, aged 28, single, was admitted to the First Medical Division, Feb. 15, 1923, complaining of swellings in the neck of two and one-half months' duration. Her family history was negative. Two years before, a physician noticed enlarged lymph nodes when he incised "boils" in both axillae. About two and one-half months before admission, the patient had noticed swellings on both sides of the neck; these were never painful or red. About the same time she had some difficulty in breathing. She was told that she was anemic, and was given a tonic. The dyspnea subsided in about two weeks. Lately she had noticed that the abdomen was gradually increasing in size, especially in the upper part, where there was marked discomfort.

The patient was fairly well developed and well nourished; the tonsils were cryptic and buried; there was a marked enlargement of all the lymph nodes, especially in the posterior triangles. The nodes varied in size from a pea to a walnut and were discrete, freely movable and not tender. The preauricular nodes were also enlarged. The chest was of symmetrical expansion. There was a slight bulging of the upper part of the sternum at the level of the second left interspace. The lungs were clear and resonant throughout. The heart was apparently normal. The entire left side of the abdomen was protuberant; there was no tenderness or rigidity. The spleen was felt to be of huge size, and filled the left part of the abdomen from the level of the eighth rib to the anterior superior iliac spine and to the right 5 cm. beyond the midline. It filled the umbilical space and part of the epigastrium. It was smooth, nontender and ballotable, and moved with respiration. The liver was not felt and did not appear to be enlarged to percussion. In addition to the cervical nodes the axillary, epitrochlear and inguinal lymph nodes were also greatly enlarged.

Blood examination on admission showed: hemoglobin, 72 per cent.; red cells, 4,768,000; white cells, 6,000; platelets, 160,000; polymorphonuclear neutrophils, 71.0 per cent.; polymorphonuclear eosinophils, 3.5 per cent.; lymphocytes, 15.5 per cent.; monocytes, 10.0 per cent.

The blood Wassermann reaction was negative.

Chemical examination of the blood showed urea nitrogen, 14 mg.; nonprotein nitrogen, 35 mg.; uric acid, 4.6 mg.; cholesterin, 0.160 per cent.

Microscopic examination, by Dr. F. S. Mandlebaum, of lymph nodes excised from the neck and both axillae did not show any evidence of Hodgkin's disease, lymphosarcoma or tuberculosis. All the specimens showed the characteristic giant lymphoid hyperplasia to be described later.

The urine was negative on repeated examinations.

The roentgen-ray examination of the chest by Dr. Harry Wessler, February 17, showed a moderate enlargement of the bronchial lymph nodes, especially at the root of the left lung.

The temperature, pulse and respirations were normal.

The patient was discharged from the hospital, March 8, with a diagnosis of splenomegaly and generalized lymphadenopathy of unknown origin, and was kept under observation in the outpatient department. There the patient received sodium cacodylate, 1 grain (0.065 gm.), three times a day, subcutaneously, but without effect. She felt apparently well for ten days, and then began to cough and to complain of dull pains in the left part of the chest, especially on coughing and deep breathing. Shortness of breath developed later. Examination of the chest revealed evidences of a left pleural effusion. The patient was readmitted to the hospital, March 24. March 25, the left side of the chest was aspirated and 20 c.c. of clear amber colored fluid was removed. Examination of the fluid showed: cell content, 3,000 per cubic millimeter; polymorphonuclear neutrophils, 1 per cent.; polymorphonuclear eosinophils, 0.5 per cent.; lymphocytes, 95.5 per cent.; endothelial cells, 3 per cent.; culture, no growth; smear, no bacteria.

The lymph nodes and spleen were gradually increasing in size, although the cough and dyspnea subsided with the rest in bed. April 12, it was decided to use radiotherapy to the spleen and enlarged lymph nodes. After the very first treatment to the spleen, the condition began to improve. Further treatment every week produced some reduction in size of the spleen and lymph nodes. On her discharge from the hospital,

April 28, the signs in the left side of the chest had cleared up and the patient felt well enough to go home.

The roentgen-ray treatments were resumed in the out-patient department, being given every week at first and later at longer intervals. The spleen gradually shrank until in December it could not be felt. The lymph nodes also could not be felt after a few roentgen-ray treatments. Occasionally, new lymph nodes appeared in the neck, axilla, or groin; here again radiotherapy proved successful in dissipating them.

At present (September, 1924) the patient is apparently well and has resumed her regular work. Radiotherapy has not been used for the last four months.

CASE 2.—E. S., a woman, aged 32, was admitted to the First Medical Division, March 26, 1923, complaining of general weakness for one year and gradual enlargement of the abdomen for two months. Her family and past history were negative. Since an attack of grip, one year previous, the patient had not felt well. She became tired very easily and felt weak. Ten months before she had had some itching and pain on the left side of the lower part of the chest. For the last two months she had noticed a gradual enlargement of the abdomen, and a feeling of heaviness. She had much discomfort on the left side of the abdomen on bending.

The patient was well developed and well nourished. The lungs were resonant and clear except at the bases, where there was dulness but no abnormal breath sounds. The abdomen was protuberant. The liver was greatly enlarged, smooth and not tender, and extended from the fourth right interspace to 12 cm. below the costal margin in the mammary line. The spleen was also greatly enlarged, smooth and not tender, and extended from the left eighth interspace above to the brim of the pelvis below and to within 2 cm. of the midline anteriorly. The cervical, axillary, epitrochlear and inguinal lymph nodes were moderately enlarged.

Blood examination revealed the findings given in the accompanying table.

The bleeding time was slightly prolonged to five minutes. The clotting time of the blood was normal; the tourniquet test and the clot retraction were normal.

The fragility of the red cells was normal.

The phenoltetrachlorphthalein liver function test showed no impairment of liver function.

The blood Wassermann reaction was negative.

Examination of the blood showed urea and nonprotein nitrogen normal; uric acid, 4; cholesterin, 0.142 per cent.

Bilirubin in the blood was normal (1:400,000).

Urobilin excretion in the urine was 135 mg.; stool from 6 to 8 gms. Later the urobilin diminished and became normal in the urine but always remained very high in the stools before splenectomy. (The normal figure for the stool is about 500 mg.)

The pathologic report of the lymph nodes corresponded to the lesion described later.

Because of the increasing weakness, progressive anemia and evidence of marked blood destruction due to the enlargement of the spleen (associated with increased urobilin excretion in the stools), it was decided to do a splenectomy to improve the condition of the patient. The splenectomy was done, May 12, by Dr. A. A. Berg.

The operation was followed by a stormy course. A pneumonia of the left lower lobe developed immediately after the operation. This was followed by a subphrenic abscess, June 5, requiring an incision and drainage. The temperature did not subside with this procedure. Typhoid fever was suspected, June 13, by the appearance of a roseola, and the suspicion was verified when a positive blood culture of *Bacillus typhosus* was obtained. The patient made an uneventful recovery after two relapses and left the hospital, August 23, in excellent condition. The patient returned for observation in the out-patient department. The lymphadenopathy disappeared about three months after the splenectomy. During December, the lymph nodes in both axillae again became enlarged, a few reaching the size of a walnut. Roentgen-ray treatment to the right axilla caused them to disappear in that area, and the lymph nodes in the left axilla are now only barely palpable. The patient has gained considerably in weight and feels well. The blood examination at present is normal except for a high platelet count.

GENERAL CONSIDERATIONS

Etiology.—The cause of the hyperplasia of the lymphoid tissue in these cases is still unknown. Whether it is due to toxic elements arising from within or without the body or to nutritional disturbances cannot be determined.

Symptoms.—The increase in the size of the lymph nodes and spleen results in the following symptoms:

1. Appearance of swelling in neck and other regions of the body. This is due to a generalized lymphadenopathy. The lymph nodes vary in size from a pea to a walnut and are discrete and not tender.
2. Dyspnea.
3. Cough. (The dyspnea and cough are due to pressure from lymph nodes in the mediastinum on the roots of the lungs.)
4. Increase in size of the abdomen due to the enlargement of the spleen. This organ extended to the pelvic brim in our patients. In one case this was associated with marked blood destruction. Occasionally pain is felt in the left hypochondrium.

Pathology.—The first patient of this series died following splenectomy; unfortunately, no necropsy was obtainable. Our third patient also had a splenectomy performed, and in the removal an intra-abdominal lymph node was included. Our pathologic study was therefore confined to two spleens and two intra-abdominal lymph nodes and to cervical and axillary lymph nodes from the two living patients.

The gross and microscopic appearances of the lymph nodes and spleens in the cases studied by us were so similar as to make individual detailed descriptions unnecessary.

Apparently, all lymph nodes throughout the body are enlarged, their size varying from that of a pea to an occasional one that may have the dimensions of a plum. The average one is about the size of a cherry. Each node is perfectly discrete and freely movable in the surrounding tissues.

When a node is excised and examined grossly, as was done in all our cases, the capsule always appears to be intact and uninvolved by disease. The consistency of the node is firm and elastic. On section, the tissue is pinkish gray and moist, and it tends to swell out above the level of the cut surface. Examined more minutely with a hand lens, the individual follicles are seen to be responsible for this projection above the cut surface, for they are enormously enlarged. Most of them are macroscopically visible, and some are as large as a pinhead. Because of their great hypertrophy, they have come to lie in close contact with one another, and the consequent crowding results in compression of the periphery and actual faceting of adjacent surfaces of contiguous follicles. The entire node therefore consists of a tightly packed mass of enlarged lymphoid follicles.

Microscopically, the picture is equally striking and cannot easily be confused with ordinary follicular hypertrophy or with the picture seen in lymphatism. Individual follicles may occupy several microscopic fields even when viewed with the low power objective and a No. 3 ocular. They are seen to lie in such close contact with one another that little or no intervening pulp is visible in most parts of the node, and the lymph sinuses are for the most part obliterated by compression.

Viewed under higher magnification, at least 96 per cent. of each follicle is seen to consist of an endothelioid type of cell. These cells are irregularly polygonal, larger than a lymphocyte, and with much more cytoplasm. Their nuclei are pale staining, although they possess a sharply staining outline and contain granules or a fine network of chromatin. The cells look like lymphoblasts and appear to be identical with those seen in the germinal centers of lymphoid follicles, especially in young children.

Adult lymphocytes with their smaller cell body and pyknotic nuclei are relatively few, and are almost exclusively confined to the edges of the follicles. They form a conspicuous narrow band of more deeply staining cells, which outlines the periphery of each follicle. In fact, the lymphocytes of the node appear to be crowded out by the enormously enlarged germinal centers.

The spleen is enormously enlarged so that it occupies a large part of the left side of the abdomen; one (Case 2) weighed 1,800 gm. and measured 7 by 17 by 28 cm. The capsule of the organ is smooth and thin.

The cut surface of the spleen presents a striking appearance, unlike that in any other form of splenomegaly. One is immediately impressed with the dimensions of the malpighian bodies. Some measure 3 mm. in diameter and are roughly the size of a barley grain. Others are smaller. These gray nodules stud the cut surface of the organ so thickly that in some places they are seen to lie in close contact with one another so as to give the appearance of being confluent. The intervening pulp appears grossly unchanged except for some congestion.

The gross appearance of the spleen is quite unlike that seen in leukemia of either the lymphatic or the myeloid type; nor can the appear-

ance be confused with miliary tuberculosis, for these giant malpighian bodies are much larger than miliary tubercles.

The microscopic picture resembles that seen in the lymph nodes, except that the average malpighian body is three or four times as large as the large lymphoid follicles of the nodes. Almost the entire malpighian body is likewise made up of lymphoid and endothelioid cells—cells with considerable cytoplasm and containing pale staining nuclei rich in chromatin. As in the lymph nodes, these enormous germinal centers are surrounded by a narrow zone of lymphocytes.

The intervening pulp appears to be markedly congested. The sinusoids are dilated. But the pulp is less cellular than normal, most of the lymphocytes being confined to the periphery of the malpighian bodies. In one spleen, the reticular tissue was distinctly increased; in the other, it was unchanged.

Hypertrophy of the malpighian bodies can be observed in patients with lymphatism and as an incidental finding in children suffering from a variety of diseases, chiefly of infectious nature. Even in adults, it is not uncommon in the absence of lymphatism to find enlargement of the malpighian bodies of the spleen after prolonged chronic infections of a low grade type, as, for example, in persons dying after a prolonged bacteria-free stage of subacute bacterial endocarditis. But such hypertrophy of the lymphoid structures of the spleen never even begins to approach the degree observed in our cases of splenomegaly.

Treatment.—Radiotherapy is the only method that produces complete disappearance of the lymph nodes and causes a reduction in the size of the spleen to normal. Arsenic is ineffectual. According to our limited experience, once reduced by adequate roentgen-ray treatment, the spleen and lymph nodes do not enlarge again.

CONCLUSIONS

1. The hitherto unrecognized disease entity of splenomegaly and generalized lymphadenopathy to which attention is called here is characterized by a giant lymph follicle hyperplasia of the lymph nodes, and by a similar pathologic process of the malpighian bodies in the spleen, resulting in an enormous splenomegaly.

2. The blood picture is normal, and the condition is apparently benign.

3. Roentgenotherapy effects a complete disappearance of palpable lymph nodes and reduces the spleen to normal size, and restores the patient to health; we cannot say as yet that it cures the disease.

The Mortality and Late Results of Subtotal Gastrectomy for the Radical Cure of Gastric and Duodenal Ulcer*

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It is well, at the very outset of this paper, to state emphatically that ulcer of the stomach is the same disease as ulcer of the duodenum. So far as we know, an ulcer situated in either viscus depends upon the same causes for its formation, has the same life history, is amenable to the same methods of treatment, and in the chronic stages can be radically cured in only one way, and that is by surgical operative methods. This statement is made because it has become the practice of a good many internists and surgeons to deal with ulcer of the stomach as though it were an entirely different disease from ulcer of the duodenum. Thus, for example, a great many surgeons advise and carry out a subtotal gastrectomy for the radical cure of gastric ulcer but strongly object to this operation for the radical cure of duodenal ulcer. Such surgeons are perfectly willing to resort to deforming and mutilating operations upon the stomach to get rid of a gastric ulcer but they are unwilling to employ such mutilating and deforming operations on the stomach for the radical cure of duodenal ulcer. It would seem logical that if a particular kind of operation is used to bring about a cure in gastric ulcer the same kind of operation should be employed to bring about this result in a similar disease when it is situated in the duodenum.

It must be clearly understood that in our clinic, operation for ulcer of the stomach and duodenum is undertaken only after repeated failures of medical treatment to cure. The patient with ulcer of the stomach or duodenum is always referred to the internist for one or more dietary and medicinal treatments and only when these fail to cure or alleviate is operation advised. Of course, sudden perforation is treated at once by operation and the individuals who have cicatricial stenoses and deformities of the stomach as a result of an ulcer have had the benefit of medical treatment prior to the time they come to us.

Up to 1920, we followed, in our clinic, the customary methods of treatment for the cure of gastric and duodenal ulcer. We employed, at various times, the operations of gastroenterostomy, ulcer excision, cautery puncture, and pyloroplasty. These operative procedures did not give us satisfactory *late results*. We found, in our follow-up of these patients, that only about 50 per cent. were cured and that at least 30 per cent. developed new ulcers at the gastroenteric stoma or had recurrent ulcers at the site of the original lesion. These results were published by my colleague, Doctor Lewisohn. They were substantiated by the results of a number of continental surgeons, notably Bier, Payr, Von Haberer, and others. We found, in our follow-up investigations (and this should be continued for ten years), that patients who had been subjected to one or the other of these operations were frequently much worse off than they had been before operation. Their sufferings were much

* Reprinted from *Ann. Surg.*, 92: 340–359, 1930, with permission of the publishers. To conserve space it has been necessary to delete all figures, including those illustrating operative procedure, and to omit substantial portions of the text.

In proposing subtotal gastrectomy as standard surgical treatment for gastric and duodenal ulcer resistant to medical management, following the lead of the continental surgeons, von Haberer and Finsterer, but with his own improved operative procedure, Berg became the center of a storm of controversy in this country. After two decades the storm has subsided. Berg's contentions and results, as outlined in this paper, have been almost universally confirmed.

A. B. G.

more severe, and, whereas before these operations had been performed they had obtained some relief from medical treatment, no such relief was obtainable from diet and medication when new ulcers formed at the new stoma or recurrent ulcers developed at the site of excision or pyloroplasty.

The disappointing late results of these operations and the equally disappointing late results of medical treatment led us to seek for new methods that would afford a lasting cure. If our conception of the factors concerned in the development of an ulcer was basically true, then any operation which was to be applied for the lasting cure of gastric or duodenal ulcer would, of necessity, have to remove these factors; namely, it would have to remove the chronic specific gastritis, it would have to render the stomach anacid, and it would have to do away with the secondary infection. The procedure that would most nearly satisfy these conditions was a partial or subtotal gastrectomy.

We had sporadically performed partial gastrectomy for gastric and duodenal ulcer since 1900 and we were impressed by the fact that patients who had been subjected to a partial gastrectomy were cured of their disease. In Germany and Austria this operation was gaining markedly in favor, especially by Von Haberer and Finsterer, and we determined to employ this operation as routine procedure for the cure of gastric and duodenal ulcer. We came to this decision in 1920.

At that time there was no standardized plan of carrying out this operation. The operation, of course, is to be divided into two parts: *first, the removal of the antrum and part of the body of the stomach, together with the pylorus and affected portion of the duodenum;* and, *secondly, the reëstablishment of the connection between the stomach and the duodenum or jejunum.* The first part of this procedure had been approached in different ways by different operators. Some advised removing the first portion of the duodenum, pylorus, antrum, and portion of the body of the stomach in a retrograde fashion; that is, from the duodenum towards the upper end of the stomach. Others recommended commencing at the upper end of the stomach and removing the same parts from above downward. Some opened the duodenum and with the finger inside its lumen peeled out the perforated, adherent, ulcerated portion of this viscus from the head of the pancreas and neighboring structures. The points of danger in the removal of this portion of the stomach and duodenum were not known or dwelt upon. It was necessary, therefore, to establish a definite method of procedure that would have in view a safe and speedy removal of the portion of the stomach, pylorus, and duodenum.

As regards the second part of the operation, *viz.*, the reëstablishment of the gastroenteric circulation, here again various operators followed different methods of procedure. Von Haberer used the method of Billroth No. 1; namely, end-to-end gastroduodenostomy, and he reported good results therewith. Later on, he found that this method was not applicable to all cases of duodenal ulcer because frequently the ulcer was situated below the normal peritoneal investment of the duodenum. In such cases he used gastroduodenostomy, end-to-side, implanting the cut end of the stomach into the side of the duodenum. Finsterer, on the other hand, was using the method of Billroth No. 2 with gastrojejunostomy. Some operators were making a gastrojejunal ante-colic (long loop) anastomosis, while some made it retrocolic with no loop. Some combined jejuno-jejunal anastomosis with a gastrojejunal implantation. Some operators used Murphy buttons for the anastomosis.

With an open mind we approached the subject of how to reëstablish the gastroenteric circulation. In 1921, 1922, and part of 1923 we used successively the various methods of gastroduodenal and gastrojejunal anastomosis. We were not at all satisfied with the results of the Billroth No. 1 or of the Billroth No. 2 either as regards motility of the stump of the stomach or as regards the applicability of the Billroth No. 1 to deep penetrating ulcers of the duodenum. We employed each one of these methods of anastomosis in a number of cases and observed the results both as regards motility and function of the stomach. The Murphy button was the least satisfactory. Though, by its use, ten to fifteen minutes of time were saved, and though it could be employed in cases where the ulcers were situated high at the cardia and the usual suture methods of anastomosis were entirely non-applicable, still, its routine use was not attended with satisfactory results. The lumen of the button would often become closed by gastric secretions or by a little blood; patients would vomit and it seemed as though post-operative pneumonia was more common with this than with the other methods of anastomosis. Thus we

went from one type of anastomosis to another until, in November, 1923, we independently devised the method of gastrojejunal implantation which we subsequently found had been described and pictured by Kronlein and Hofmeister. Almost from the first the procedure gave us very satisfactory results and from November, 1923, we adopted it as routine anastomosis between the stump of the stomach and the first portion of the jejunum. The entire operation—removal of a portion of the body, antrum, pylorus, and affected portion of the duodenum—and the method of reëstablishing the anastomosis between the stomach and jejunum, according to the descriptions of Hofmeister, were published by me in the Surgical Clinics, in 1925.

As shown in the illustrations, the operation commences at a definite point (the ligation of the cardiac artery) and proceeds from that point straight ahead in successive stages until the desired portion of the stomach and duodenum has been removed and then a gastrojejunal anastomosis is established according to the method of Hofmeister. This routine, standardized procedure is deviated from only when local conditions demand it. There are a number of "don'ts" that must be strictly observed. First, and principally, too much stress cannot be laid upon avoiding entrance within the pancreatic capsule while mobilizing the duodenum. Such an act opens the door to infection of the pancreas and its consequent evil, frequently fatal, results. Ulcers that penetrate within the capsule of the pancreas are usually surrounded by an inflammatory wall and it is highly important to keep inside the limits of this inflammatory wall. Again the bed of an ulcer, penetrating on or into the head of the pancreas, must be well cleaned with iodine. Especially important is it to avoid any hematoma around the head of the pancreas or around the duodenal stump. Such hematomata frequently become infected and thus occasion pancreatitis, peritonitis, duodenal fistulæ, *etc.* Finally, it is very important to cover over all the raw areas left in the dissection by sewing the upper layer of the transverse mesocolon to the anterior wall of the duodenum so as to prevent accumulation of secretions in these raw spaces. Such secretions easily become infected and, in their turn, give rise to peritonitis, fistulæ, etc.

The closure of the duodenum must be done with meticulous care. The first layer of sutures is a through-and-through mattress one, passed from without in, and *the mucous membrane must be carefully turned in at all points.* The second layer of sutures may be passed either in purse-string fashion, where there is enough peritoneal surface of the duodenum left behind, or the capsule of the pancreas is sewn over to the anterior duodenal wall, thus buttressing the first layer of sutures with the head of the pancreas. If the duodenal suture is carefully carried out, no duodenal fistulæ will result.

Care must be taken not to injure the middle colic artery. This accident can be avoided if the transverse mesocolon is separated from the posterior wall of the stomach before any clamps are applied.

The avoidance of hæmorrhage from the cut end of the stomach can be accomplished *in only one way;* namely, by grasping the blood-vessels in the wall of the stomach individually and separately, and tying each one of such vessels. Post-operative bleeding into the stomach may be immediately fatal or it may favor a fatal issue by aspiration of blood into the lungs during vomiting or by materially reducing the resisting power of the individual.

As has been said above, we have followed this standardized routine procedure from November, 1923, and it is to the results obtained in the use of this operation for the radical cure of gastric and duodenal ulcer that I invite your attention. In the first place, to the *immediate operative mortality.* It is important to state at this point that at Mount Sinai Hospital, where the cases reported in this paper were done, we recognize no difference between hospital mortality and operative mortality. The patient is discharged from Mount Sinai well or dead. It is utterly immaterial how long the patient stays in the hospital. If he dies weeks or months after the operation the death is recorded as an operative death and all these statistics must be viewed in that light.

Total number of primary and secondary operations for ulcer of stomach and duodenum and gastrojejunal and jejunal ulcers:

Ward Service, December, 1923–December, 1929	Primary operations	233
	Secondary operations	81
Private Service, January, 1924–December, 1928	Primary operations	178
	Secondary operations	24
		516

Total number of *primary operations* for ulcer of stomach and duodenum, 411. Of these

Six were at cardia or juxta-cardia

405 were in the stomach below cardia or in the duodenum

Total number of *secondary operations* for recurrent gastric and duodenal ulcers and gastrojejunal and jejunal ulcers, 105

Mortality in primary subtotal gastrectomy

Total number of cases	405
Total number of deaths	32

7.9 per cent.

Properly exclude from this operative mortality:

1 death—puncture of lung by interne during subcutaneous saline infusion

1 death from transverse myelitis. (Six weeks after operation autopsy showed abdominal viscera entirely healthy)

1 death—pathological, pre-operative, duodeno-choledochal fistula with cholangitis

1 death—patient with *active tuberculosis* in whom operation had been repeatedly rejected by surgeon.

Thus leaving

Total of cases	401
Total deaths	28

6.9 per cent. mortality

This mortality includes every death following primary subtotal gastrectomy during six years of ward and five years of private service.

It includes all bleeding ulcers, active or arrested, all patients with chronic pulmonary lesions, all patients with chronic cardiovascular disease, all patients with tetany, all patients with chronic renal lesions.

It is proper at this point to define what we mean by a *primary* and *secondary partial gastrectomy*. By a *primary subtotal* or *partial gastrectomy* we mean that the patient has had *no previous major gastric operation* done prior to the subtotal gastrectomy. He may have had an exploratory laparotomy, or an appendectomy, or cholecystectomy, or an exploratory gastrostomy, but we mean that there has not been a preceding gastroenterostomy, pyloric excision, pyloroplasty, or closure of a perforated duodenal or gastric ulcer. By a *secondary operation we mean that the patient has had one or more* (in our series the maximum number of preceding operations was fourteen) preceding major gastric operations such as gastroenterostomy, pyloroplasty, ulcer excision, *etc.* The reason for this differentiation is that "preceding major gastric operations" usually result in the formation of more or less dense adhesions between the stomach, omentum, liver, gallbladder, pancreas, and abdominal wall. The division of such adhesions and the development of the stomach are usually severe operations and contribute materially to shock and post-operative sequellæ. This can be seen when we study the mortality statistics in primary subtotal gastrectomy. In the former, in our own series, the operative mortality has been 6.9 per cent., whereas in the secondary operations the mortality has been 20.9 per cent.

In the past six years, we have had a number of patients with gastric ulcer situated at, or juxta to, the cardiac opening of the stomach. We call such situated ulcers "high gastric ulcers." As a rule, we operate upon these patients only when we are compelled to, because the attendant risk is exceedingly great. The compelling indications for operation are repeated severe hæmorrhages, perforation, stenosis of the cardiac opening, perigastric inflammation and suppuration. These ulcers are particularly difficult to deal with surgically because the adjoining portion of the œsophageal wall is infiltrated by inflammatory tissue, thus rendering suture difficult, and because the incidence of post-operative pneumonia is exceptionally high. We divide the operations which we have employed for the removal of such high-seated ulcers into two types—*total, or anatomically complete gastrectomy*, where the line of division goes through the lower end of the œsophagus at or above cardiac ring, and *physiological complete gastrectomy*, where the line of division goes through *one wall of the œsophagus and through the very topmost portion of the fundus*, leaving just sufficient of the fundus to hold the gastric half of a Murphy's button, by means of which the anastomosis can be readily made with the jejunum.

The time that has elapsed for the observation of patients in whom a primary subtotal gastrectomy was performed is still too short to draw any positive conclusions as to lasting cure. We have, in preceding publications, insisted upon a ten-year period of observation. The cases reported in this paper have been under close observation from one to six years. We have been able to keep in touch with about 60 per cent. of our ward patients and about 80 per cent. of our private patients. The cases reported in this paper are about 50 per cent. ward and 50 per cent. private patients. Though we are not able to report, this evening, on the late results after as long a period as with the gastroenterostomies, nevertheless, we can compare the results following gastroenterostomy, *etc.*, after six years with those that have followed partial gastrectomy after six years. Doctor Lewisohn investigated the late results following gastroenterostomy for ulcer and found them to be as follows: In 68 cases of gastroenterostomy for ulcer of the duodenum, re-

examined from 4 to 9 years, 47 per cent. were completely cured; 19 per cent. had a fair result and 34 per cent. had gastro-jejunal ulcers. The diagnosis of gastro-jejunal ulcer was confirmed by secondary operation in 18 per cent. and in the remaining 16 per cent. was based on clinical symptoms and X-ray findings. In comparison with gastroenterostomy, we have had four cases of probable recurrence of ulcer in the ward patients and two cases of definite recurrence in private patients.

We are strongly suspicious of recurrent ulcer in four ward patients but are by no means sure of it. Three of these patients are able to attend to their daily work, but have occasional periods of pain. Their gastric contents all show free hydrochloric acid. X-ray examination sometimes reveals a tender stoma, and in two there seems to be a penetrating ulcer at the new anastomosis. At other times the X-ray examinations are entirely negative. Their sufferings are so mild in character that they are unwilling to be operated upon. All three maintain or have gained in weight. We class these cases amongst the recurrent ones but, as stated above, we are not at all convinced that they belong positively in this category. The fourth ward patient is put down as a recurrent case because he complains of ulcer symptoms. Objectively, neither by physical examination nor by X-ray, have we found any evidence pointing to a recurrence. His gastric contents are subacid.

Thus, out of a total of 516 cases of primary and secondary partial gastrectomies, we have but two cases of undoubted recurrence, three cases of probable recurrence, and one case of possible recurrence. All six patients have had free hydrochloric acid in their gastric contents. If all six cases are put down as positive recurrence, the percentage would be 1.1. In a similar period, I have shown from the statistics of Doctor Lewisohn, above quoted, in the same clinic, that, with the same character of patients, with the same kind of ulcers, the percentage of recurrence was 34 per cent.

There need be very little more said when these results are compared. The patients who have had a partial gastrectomy are vigorous, strong, eat all kinds of food, are able to do their work; their intestines function, for the most part, normally, and there is a percentage of recurrent ulcer of 1.1 per cent. Those who have had gastroenterostomy, *etc.*, performed never measure up to those who have had partial gastrectomy done. While some of them eat everything, the majority must be careful of their diet and the percentage of recurrence is over 30 per cent. It is such a comparison as this that confirms our belief in the value of partial gastrectomy as a cure for gastric and duodenal ulcer.

When we commenced our work on partial gastrectomy for the cure of ulcer we had reason to believe that by the removal of the antrum the gastric contents would be rendered anacid. It was thought that the secretion elaborated by the antrum stimulated the acid gastric glands to action and that the removal of this secretion would remove the motor that caused the acid glands to secrete free hydrochloric acid. We were particularly happy in our early cases to find that after partial gastrectomy gastric secretions were anacid. At that time we were using the Ewald test meal and the meal was extracted about an hour after its ingestion. When we replaced the Ewald test meal by the fractional test meal (Rehfus), we found that gastric anacidity did not always follow upon partial gastrectomy. Dr. Eugene Klein, of our clinic, took up a careful investigation of this subject and his results are shown in the following table:

MAXIMUM FREE ACID AFTER PARTIAL GASTRECTOMY IN FRACTIONAL TEST MEALS

	Anacid	0–20	20–50	50 and above	Number of cases
Duodenal:					
Before operation	.....	4 per cent.	36 per cent.	60 per cent.	50
Recent	9 per cent.	9 per cent.	46 per cent.	36 per cent.	11
Old	25 per cent.	41 per cent.	17 per cent.	17 per cent.	12
Gastric:					
Before operation	.....	28 per cent.	60 per cent.	12 per cent.	25
Recent	45 per cent.	33 per cent.	11 per cent.	11 per cent.	9
Old	100 per cent.	.....	.....	.....	3
Gastrojejunal:					
Before operation	.....	11 per cent.	67 per cent.	22 per cent.	9
Recent	25 per cent.	25 per cent.	50 per cent.	.....	4
Old	50 per cent.	.....	50 per cent.	.....	2

("Recent," refers to cases examined immediately after operation; "old," to cases examined six months after operation; "before operation," in gastrojejunal group, refers to cases examined before partial gastrectomy.)

The results of this investigation showed us that partial gastrectomy did not always bring about an anacidity and we had long ago learned that as long as the gastric contents remained acid the possibility of recurrence existed. It will be noted from the above table that all of the gastric ulcers were followed by an anacidity of gastric contents and in no case of gastric ulcer treated by partial gastrectomy have there been evidences of recurrence. The six cases with possible recurrence referred to above have all been duodenal ulcers. It is reasonable to conclude that the higher the percentage of free acid in the gastric contents, the greater the possibility of recurrence. Patients with duodenal ulcer who have a low or moderate acidity prior to partial gastrectomy all become anacid or considerably subacid after partial gastrectomy. Thus, it is only those who have hyper amounts of acid before the operation of partial gastrectomy, that maintain this acidity after the antrum and part of the body of the stomach have been removed. It is to this class of cases that we devoted our attention, to see whether we could not render them completely anacid or markedly subacid. Doctor Winklestein approached this question in a medical way and Dr. Eugene Klein dealt with it in an experimental operative manner. Their results have been published elsewhere. We found, experimentally, that the division of the left pneumogastric nerve as it passed through the cardiac opening of the stomach rendered patients completely anacid who were highly acid prior to partial gastrectomy, and whom we had every reason to suppose would remain acid after the partial gastrectomy. Some of these patients, and there were sixteen altogether, became anacid two weeks after the operation and the rest of them became totally anacid several months after left vagus section. None of the patients in whom a left vagus section was made died or showed any untoward results. The division of the left vagus nerve at the cardiac opening of the diaphragm can be rapidly done without any added risk and with no untoward symptoms or disturbances. We do it now regularly in all patients who have high acidity prior to operation. This question will be dealt with in subsequent publications.

Quite a number of patients who suffer with gastric and duodenal ulcer present the symptoms of vagotonia prior to any operative interference. Frequently these vagotonic symptoms are more distressing than those resulting from the ulcer. These vagotonic symptoms are not at all dependent upon the ulcers but accompany them. It is readily seen, therefore, that they are not very likely to be influenced by any of the procedures that are employed for the cure of ulcer. In our follow-up clinic we see quite a number of patients who complain of dizziness, headache, sweating of the palms, cardiac palpitation, even though they are entirely free of all gastroenteric disturbances. Tonics, roborant treatment of all kinds, and sunlight treatments are all of help in ameliorating this type of complaint. We have not seen that the patients are incapacitated from their usual occupations by the existence of these vagotonic disturbances.

In this series of 516 patients there were quite a large number who came to us in the active period of bleeding. In a considerable percentage of these cases the hæmoglobin had fallen to 20 to 30 per cent. It is not our practice to operate in the active stage of bleeding unless the bleeding is persistent and continuous. It is our practice to wait until hæmorrhage stops and then, after one or more transfusions, to proceed to operate. In three of the patients of this series we were compelled to operate because the hæmorrhages had been persistent for three weeks or more, even though the individuals were in a practically moribund condition. All three of these patients died. These three patients should be taken out of the mortality statistics because we knew in advance that death would ensue and it was only in the hope of saving a lost life that operation was undertaken. In all three of these cases operation should have been resorted to before the patient's condition became so desperate. When the patient is very anæmic prior to operation, either because of loss of blood or because of the pains and suffering and toxæmia resulting from the ulcer or from both combined, it takes a long time (six months to a year) before the anæmic condition is improved. Now and then a transfusion will help, but, as a rule, the slower building-up process by fresh air, nourishing food, heliotherapy, and tonic is more effective. For the first six months after the operation the patient seems to remain stationary. His blood-picture changes very little but once he commences to improve, his progress is rapid and steady. *We have not seen any case of pernicious anæmia* following *partial gastrectomy*.

Much has been said concerning the comparative results of medical and surgical treatment for the cure of gastric and duodenal ulcer. The surgeon has been content, even to the present time, to take his cases for operation from

those who have resisted repeated efforts on the part of the internists to bring about a cure and from those who have suffered from cicatricial stenoses and malformations of the stomach as the result of the healing process. The time has come when the experience of the surgeon in the radical cure of ulcer should be set side by side with that of the medical man. We believe, as do most surgeons, that the patient suffering from ulcer should have at least one thorough-going medical treatment. If this prove inefficacious, then the patient should be told that continuation of the medical treatment will serve only to relieve the symptoms, but will not be likely to effect a cure. The result of partial gastrectomy in the cure of ulcer has been carefully given in the preceding pages. It is well to glance at the late results of medical treatment. A few years ago, Dr. B. Crohn made a study of his cases in the out-patient department of the Mount Sinai Hospital, the results of which are hereby given.

The consideration of these medical results by two independent investigators shows that medical treatment fails to bring about a lasting cure in a large percentage of the patients. If the results already obtained by partial gastrectomy are further substantiated by continued observation, is it not fair to conclude that where patients have not been cured of their ulcer by one or two good medical treatments, they should be advised to undergo operation?

It is a common fallacy to believe that medical treatment of ulcer is unattended by any risk. This is not in accordance with facts. In our hospital, during a period of about ten years, about 1 per cent. of ulcer cases under medical treatment died from hæmorrhage; at least 1 per cent. died from perforation; a small percentage of gastric ulcers developed carcinoma. Quite a large percentage of patients, while under medical treatment, die from inanition, toxæmia, and renal, cardiac, and pulmonary complications. If all of these causes of death are counted up the mortality attendant upon palliative medical treatment of ulcers is considerably

REMOTE RESULTS OF MEDICAL TREATMENT IN PERCENTAGES

Year	Cases	Period of Follow up	Cured	Impr.	Unimpr.	Oper.	Perforation	Death
1922	22	4 year	27.3	22.7	9.1	31.8	9.1	4.5
1923	17	3 year	41.2	23.5	5.9	23.5	0.	5.9
1924	30	2 year	56.6	10.	6.6	23.3	0.	3.3
1925	32	1 year	67.5	22.	9.4	1.1	0	0

A larger number of cases was analyzed by Nielsen, and the results published in the Acta Scandinavia.

ULTIMATE RESULTS OF MEDICAL TREATMENT OF GASTRIC AND DUODENAL ULCER
2½ to 20 years after discharge from hospital. (Nielsen)

Duration of Symptoms	Permanently Cured	Permanently Cured after Relapse	Total Permanently Cured	Improved	Bad Results
Symptoms less than ½ year before treatment 30 cases	60 %	0	60 %	16.7%	23.3%
Symptoms ½ to 1 year before treatment— 24 cases	33.3%	20.8%	54.1%	16.7%	29.2%
Symptoms 1 to 3 years before treatment— 19 cases	26.3%	10.6%	36.9%	21 %	42.1%
Symptoms 3 to 5 years before treatment— 15 cases	20 %	0	20 %	26.7%	53.3%
Symptoms 5 to 10 years before treatment— 37 cases	2.7%	8.1%	10.8%	10.8%	78.4%
Symptoms over 10 years before treatment— 35 cases	5.3%	0	5.3%	17.6%	77.1%

higher than that attendant upon the radical surgical treatment.

In concluding this paper the writer wishes to call attention to several important facts concerning ulcer. Firstly, ulcer of the stomach and duodenum is a local disease dependent upon a specific gastritis, free hydrochloric acid in the stomach contents, and a secondary infection. Secondly, a radical cure must eliminate all of these factors. Thirdly, experience has shown that partial gastrectomy, because it eliminates all of these factors, is most likely to effect a radical cure. The number of recurrences after partial gastrectomy is exceedingly small—about 1 per cent. Finally, investigation has shown that the medical treatment of ulcer is attended by just as grave risks as is surgical treatment, and, unless instituted very early, is not likely to bring about radical cure; and that when a patient has had one or two good medical treatments and has not been cured, operative procedure should be undertaken.

Regional Ileitis*

A Pathologic and Clinical Entity

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We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

The disease is clinically featured by symptoms that resemble those of ulcerative colitis, namely, fever, diarrhea and emaciation, leading eventually to an obstruction of the small intestine; the constant occurrence of a mass in the right iliac fossa usually requires surgical intervention (resection). The terminal ileum is alone involved. The process begins abruptly at and involves the ileocecal valve in its maximal intensity, tapering off gradually as it ascends the ileum orally for from 8 to 12 inches (20 to 30 cm.). The familiar fistulas lead usually to segments of the colon, forming small tracts communicating with the lumen of the large intestine; occasionally the abdominal wall, anteriorly, is the site of one or more of these fistulous tracts.

The etiology of the process is unknown; it belongs in none of the categories of recognized granulomatous or accepted inflammatory groups. The course is relatively benign, all the patients who survive operation being alive and well.

Such, in essence, is the definition of a disease, the description of which is based on the study, to date, of fourteen cases. These cases have been carefully observed and studied in their clinical course; the pathologic details have resulted from a close inspection of resected specimens from thirteen of fourteen patients operated on by Dr. A. A. Berg.

RELATIONSHIP OF REGIONAL ILEITIS TO OTHER BENIGN INTESTINAL PROCESSES

There exists in the medical literature a heterogeneous group of benign intestinal lesions which have now and then been described under the caption of "benign granulomas." The latter loose term covers a multiplicity of conditions in which both large and small intestines may be involved; it includes all chronic inflammatory lesions of the intestine whose etiology is either unknown or attributable to an unusual physical agent. It represents a hodge-podge or melting-pot in which are thrown all those benign inflammatory intestinal tumors which are neither neoplastic nor due to a specific bacterial agent. Within this group one finds descriptions of foreign body tumors, chronic perforating lesions with gross inflammatory reactions, traumas of the mesentery with intestinal reactions, Hodgkin's granuloma, a late productive reaction to released strangulated hernias of the intestinal wall and numerous other and similar conditions. The so-called benign granulomas all present a tumor-like inflammatory mass which usually simulates carcinoma but which eventually unmasks itself as probably an infectious process of unknown causation. The multiplicity of the possible sites of gastric, intestinal or colonic involvement and the accompanying protean clinical manifestations defeat any effort to include them all in a clear cut clinical entity. The very confusion defies classification.

In this literature, however, there have appeared on occasions references and descriptions that approach the picture that we are about to

* Reprinted from *J. A. M. A.*, 99: 1323–1328, 1932, with permission of the publisher. One figure has been omitted.

This classic paper gives the first clear and comprehensive description of an entity, regional ileitis, which the authors segregated from the heterogeneous group of "benign granulomas" of the intestine. A. B. G.

describe. The entire literature of benign granulomas was reviewed in 1920 by Tietze,[1] who not only described his own cases but covered all previous medical publications. There is nowhere in his encyclopedic article a description which resembles that of regional ileitis. In 1923, Moschcowitz and Wilensky,[2] in describing four cases of benign intestinal granuloma, detailed one case of a disease involving the terminal ileum which closely resembled that in our cases. They grouped it with various other and similar colonic masses as granuloma. Mock[3] in 1931 again described granuloma, but included no example that resembled the cases we have studied.

Just as the generic term of typhus originally included various diseases, from which group eventually typhoid fever, Brill's disease, Rocky Mountain fever, tabardillo and others were split off, so, similarly, do we aim to disintegrate from the general group of varied diseases spoken of as a "benign granuloma" a specific clinical entity with constant and well defined characteristics, which we propose to name "regional ileitis."

PATHOLOGY ANATOMY OF THE DISEASE

All the specimens obtained by resection were in patients who had been ill for at least a year. We therefore have no specimen exhibiting the very early phases of the disease. The latter are sometimes encountered at the operating table following an illness of from one to two weeks and diagnosed, as a rule, as acute appendicitis. At this time the terminal ileum is found thickened, soggy and edematous; the serosa is a blotchy red. The mesentery of the terminal ileum is greatly thickened and contains numerous hyperplastic glands. Owing to the possibility of spontaneous resolution, resection has never been performed at this stage, so that we have no knowledge of the intra-intestinal changes present at this time.

The inflammatory process is not, however, a static one, nor is the entire diseased segment affected at one time. The oldest lesions begin apparently at, or just oral to, the ileocecal valve, and the more recent ones are situated proximally. In some of our relatively early cases, we have found isolated lesions separated from the main hypertrophic mass by normal mucosa. These isolated areas are, in our opinion, the earlier and primary lesions of the disease; they consist of oval mucosal ulcerations, about 1 cm. in diameter, located on the mesenteric border of the small bowel and lying in the long axis of the intestine, where a sort of groove is naturally formed by the attachment of the mesentery.

The characteristic, fully developed hypertrophic process is, as a rule, limited to the distal 25 to 35 cm. (10 to 14 inches) of the terminal ileum, including the ileal side of Bauhin's valve and terminating rather abruptly at that point. The most advanced pathologic changes are present at the valve, which in some instances becomes converted into a rigid diaphragm with a small irregular opening. Proximally the severity of the process gradually abates, shading off into normal mucosa. The normal intestinal folds are distorted and broken up by the destructive ulcerative process and rounded and blunted by edema, giving a bullous structure to the mucosal aspect of the intestine, or frequently a cobblestone appearance of the surface of the mucosa may result. A series of small linear ulcerations lying in a groove on the mesenteric side of the bowel is almost always present. Whether these are the remnants of the original ulcerative lesions or whether they are mechanical erosions due to the formation of a *darmstrasse* by the shortening of the fibrotic mesentery, it is impossible to say.

The submucosal and, to a much lesser extent, the muscular layers of the bowel are the seat of marked inflammatory hyperplastic and exudative changes. As a result of these, the wall of the bowel becomes enormously thickened, frequently reaching two or three times its normal density. The lumen of the bowel is greatly encroached on, becomes irregularly distorted and, at times, is only large enough to admit a medium-sized probe. The intestine proximal to the involved segment frequently, but not invariably, becomes greatly dilated and may show superficial irregularly placed tension ulcers. When seen at the operating table, the involved loop is a soggy hoselike mass.

In the older phases of the disease, the exudative reaction is replaced by a fibrostenotic process, and the mucosa appears atrophic with occasional superficial erosions and islands of papillary or polypoid hyperplasia. The serosa loses its gloss and frequently exhibits tubercle-

1. Tietze: Ergebn. d. Chir. u. Orthop. 12: 212, 1920.
2. Moschcowitz, E., and Wilensky, A.: Am. J. M. Sc. 166: 48, 1923; 173: 374, 1927.
3. Mock, H. E.: Surg., Gynec. & Obst. 52: 672, 1931.

like structures on its surface. The mesentery of the affected segment is greatly thickened and fibrotic, as is the subserosal intestinal fat.

A marked feature is the tendency toward perforation. Free perforation into the peritoneal cavity has not been encountered in this series. The chronic perforation apparently occurs slowly enough to permit of walling off by adhesions to a neighboring viscus, to the parietal peritoneum or to the omentum. There is a marked tendency to the formation of internal fistulas, the sigmoid having been the seat of fistulous involvement four times and the ascending colon and cecum once each. The walled-off abscesses resulting from slow perforation into the peritoneal cavity are, as a rule, considered appendicular in origin. When drained, they give rise to chronic intractable fecal fistulas which defy attempts at simple closure because of the persistence of the underlying inflammatory disease in the bowel. Indirect perforation of the cecum may result from perforation of the ileum into the terminal mesentery with secondary cecal termination of the fistulous tract. Pericecal fibrotic and inflammatory changes which result from the proximity of the ileal focus to the cecum are probably responsible for the roentgenologic changes in the contour of the ascending colon and cecum, such as may be easily confounded with the defect of hyperplastic tuberculosis.

Microscopically, no specific features can be demonstrated. The stained histologic sections showed various degrees of acute, subacute and chronic inflammation, with variations in the predominance of polymorphonuclear, round cell, plasma cell and fibroblastic elements. In the early stages the lesion is a diffuse one, involving mainly the mucosa and submucosa, with the presence of some inflammatory serosal reaction. The mucous membrane shows areas of marked destruction, and at times the glandular structure is almost completely gone, leaving an atrophic layer of epithelium, the result of a regenerative process. In later stages of the disease, the inflammatory reaction is more focal in character. These focal areas of inflammation in the serosa give the appearance, on gross examination, of tubercles.

In some of the cases, the presence of giant cells is quite striking. Special stains have occasionally demonstrated the presence of large pale cells, or groups of cells, probably vegetable in nature, in the vicinity of the giant cells. They could be demonstrated frequently in all the layers of the intestine. These and the giant cells are probably not an essential feature of the pathologic changes in this condition. They are, more likely, accidental findings due to the inclusion of small particles of vegetable matter which have become entrapped in the ulcers, entered the lymphatics and become encapsulated in the process of healing. The resultant foreign body reaction around these nonabsorbable particles results in the presence of the giant cells. To some extent they may be contributory to the marked hypertrophic scarring which occurs. We believe that the attempts, by some authors, to classify this granulomatous condition as an unusual form of tuberculosis were, to a great extent, predicated on the assumption that the giant cells were, necessarily, evidences of tuberculosis.

It is quite likely that in the past this granulomatous condition was confounded with ileocecal tuberculosis, and so missed as a clinical and pathologic entity. The failure of the pathologic reports in our cases to substantiate a suspicion of tuberculosis led us to exercise still greater caution in eliminating a Koch infection as the etiologic agent. With the assistance of Dr. Paul Klemperer in determining moot points, sections from the various cases were again reviewed. No evidences of tuberculosis, syphilis, actinomycosis, Hodgkin's disease or lymphosarcoma were found. Guinea-pig, rabbit and chicken inoculations of triturated material from mesenteric glands and from the intestinal wall proved negative for tuberculosis in five cases. Löwenstein tubercle cultures were also negative in three instances. It is interesting to note that none of these clinical cases presented any evidence of pulmonary tuberculosis; there were no positive Wassermann reactions in this series.

The relation of appendicitis and previous operations to the development of the disease is of some interest. Half of the patients had been subjected to appendectomy before the final resection was performed. In about half of those cases, abnormalities of the terminal ileum were already noted at the time of that operation. In those cases in which there had been no previous appendectomy, the mucosa of the appendix was not involved, as might be expected from the fact that the disease stops on the ileal side of the valve. Inflammation of the outer coats of the appendix, due to the presence of adjacent inflammatory disease, was common.

THE CLINICAL FEATURES

Etiologically, young adults comprise the largest number of patients. Only two of the patients studied were over 40 years, the average incidence being at 32 years of age; the youngest patient was 17, the oldest 52. Males predominate over females in the proportion of nearly 2:1. There are no known predisposing factors.

Cases of regional ileitis run, in general, a fairly constant and typical clinical course. Most of the patients had been ill for from several months to two years before coming under observation. During this time the outstanding complaints were fever, diarrhea, continuous loss of weight and a progressive anemia. The clinical picture resembles that of a nonspecific ulcerative colitis.

Fever is rarely high, long periods of apyrexia being interspersed with shorter and irregular cycles of moderate temperature. Occasionally, though rarely, the temperature rises above 103 F. Some of the cases run the complete course without fever.

Diarrhea is usually an outstanding feature, though the number of movements and the intensity of the actions never approach those of a true colitis. The average patient has from two to four loose or semisolid daily defecations, sometimes with blood and always with mucus. The stools are rarely mushy or liquid and contain free pus, coagulated lumps of mucus and streaks of blood, but tenesmus is always lacking. There are none of the perianal fistulas, condylomas or perirectal abscesses that characterize the complications of true colitis, for in this disease the rectum and colon are never involved. At times, particularly when the stenotic factor predominates, as in the later periods of the course, constipation rather than diarrhea predominates.

Vomiting characterizes the stenotic type of cases, is never marked or persistent and is usually accompanied by abdominal pain and visible peristalsis.

Pain distributed over the lower abdominal parietes is a common feature of the disease. This pain is full and cramplike and accompanies, or is followed and relieved by, defecation. It is usually localized to the right lower quadrant and is occasionally referred across the abdomen to the whole lower abdominal region. Occasionally, and not infrequently, when the sigmoid, as is not unusual, becomes adherent to the necrotizing hyperplastic ileum, fistula formation occurs between these two hollow viscera. In these cases the pain is mainly localized over the left lower abdominal quadrants; the mass which is then felt abdominally and per rectum may appear to be an integral disease of the rectosigmoid area.

The general symptoms are those of weakness, usually a rapid and progressive loss of weight, and an anemia which ordinarily is moderate, but which may progress to a severe degree. In the milder cases, however, there may be little or no emaciation and anemia. The stools contain constantly occult blood. Appetite is poor, particularly during the febrile bouts.

A moderate leukocytosis characterizes some of the cases; in most, the white blood count is normal. Even in the stenotic cases the blood plasma findings that accompany marked obstructions of the upper alimentary tract are rarely seen.

PHYSICAL EXAMINATION

Certain physical findings characterize this disease, the most constant ones being (1) a mass in the right iliac region, (2) evidences of fistula formation, (3) emaciation and anemia, (4) the scar of a previous appendectomy and (5) evidences of intestinal obstruction.

1. A moderate-sized mass is usually felt in the lower right iliac region or in the lower midabdomen. The mass is usually the size of a small orange, tender, firm, irregular and only slightly movable. This mass is composed of the tremendously hyperplastic ileum, the stenotic inflamed ileocecal junction, which may and often does assume a size of from two to five times that of a normal valve of Bauhin, and frequently an adherent section of the colon or sigmoid to which a fistulous tract has been created. When the sigmoid is adherent and involved, the mass may lie more to the left; when the cecum or ascending colon or hepatic flexure constitutes the distal end of the fistulous tract, the mass may lie more to the right and higher in the abdomen. When the fistulous tract burrows into and through the mesentery, the necrotic process may cause a diffuse mesenteric suppuration which participates in the formation of the mass. The tumor is usually palpable per rectum, though felt only very high with the examining finger.

2. Fistula formation is a constant feature of the disease process. The most common site of

adherence is the sigmoid; next in frequency is the cecum and the ascending colon and occasionally the hepatic flexure. As the necrotizing process of the mucosa of the ileum progresses through its several coats, the serosa becomes involved. Any hollow viscus, usually the colon, now becomes adherent to the point of threatened perforation. A slowly progressive perforation is thus walled off, but results in a fistulous tract being formed between the two viscera. In one case the uterus formed the limiting organ of a threatened perforation. In another case, on sigmoidoscopic examination, a nipple-like papillomatous projection was seen high in the rectum, or just above the rectosigmoid angle. This observation was noted at the time, but the proper interpretation was overlooked, it was the colonic end of a perforating fistulous tract. In still another case, the anterior abdominal wall presented a fecal fistula, particularly such as persists after a fruitless appendectomy. These fistulas are usually regarded as cecal in point of origin; they are always, however, communications between the necrotic ileum and the anterior abdominal wall.

3. There are evidences of emaciation and anemia.

4. In at least half of the cases the appendix had been removed at some previous operation. This appendectomy usually antedated by several months or years the present symptoms. In many cases the appendix had been removed several months previous, at which time thickening and tumor-like massive inflammation of the small intestine and mesentery had been noted, though nothing beyond the appendectomy had been attempted. It seemed quite evident that in these cases the lower right abdominal symptoms had resulted in the discovery or in the overlooking of the real pathologic process in the terminal ileum. In all such cases the pathologic report cited "acute and chronic inflammatory changes of the appendix," a report which really whitewashed this organ as a participant in the disease process. In fact, we now know that the process never transcends the limit of Bauhin's valve, and that the appendix is always free from guilt and free from changes.

5. In those cases in which the process has progressed to a stenotic stage, the physical findings are those of intestinal obstruction. Loops of distended intestine may be visible through the emaciated abdominal wall, and puddling is frequently observed in the flat x-ray plates. Visible peristalsis is not uncommon and is accompanied by borborygmus and the passage of gas with evident relief. The visible loops of the distended intestine are usually localized to the lower midabdomen. General distention and ballooning of the whole abdomen are unusual.

CLINICAL COURSE OF THE DISEASE

There are four various types of clinical course under which most of the cases may be grouped: (1) acute intra-abdominal disease with peritoneal irritation, (2) symptoms of ulcerative enteritis, (3) symptoms of chronic obstruction of the small intestine and (4) persistent and intractable fistulas in the right lower quadrant following previous drainage for ulcer or abdominal abscess.

1. *Signs of Acute Intra-Abdominal Inflammation.*—It is impossible to distinguish these cases preoperatively from those of acute appendicitis. There are generalized colic, pain and tenderness in the right lower quadrant and fever up to 101 or 102 F. The white blood count is elevated. The development of symptoms seems to be somewhat slower than in appendicitis. The presence of a mass even without actual abscess formation is a fairly constant feature. The picture encountered at operation is that of a greatly thickened, red or blotchy terminal ileum, with marked edema of the surrounding tissues and slight exudate of the ileal wall. The mesentery is thickened and edematous, and contains numerous large glands. There is usually clear fluid present in the abdomen. The appendix may appear, and shows evidence of a periappendicitis without mucosal involvement. In some cases an abscess is encountered; in our experience the pus has been thick and grumous, and not as foul smelling as an abscess of appendiceal origin. The future course of these cases cannot be predicted. Some seem to undergo resolution, others to pass into one of the more chronic phases of the disease. Those cases which are drained may develop intractable fistulas.

2. *Symptoms of Ulcerative Enteritis.*—These patients complain of colicky periumbilical or lower abdominal pain. There is a tendency toward looseness of the bowels (from three to five movements a day). The stool is usually liquid or mushy and contains pus, mucus and occult or visible blood. There is no gross melena. A constant fever is present, but the temperature is rarely above 100 F. With the progress of the

disease, a marked secondary anemia may develop, reaching as low as 35 per cent hemoglobin. Considerable loss of weight and strength may occur. In some instances disturbances of general nutrition are slight. This course may continue for as long as a year until exhaustion sets in, or more commonly the cases pass gradually into the stenotic phase of the disease.

3. *Stenotic Phase.* This is the type most commonly encountered. The symptoms in this stage are those of a subacute or small intestinal obstruction of varying severity. The obstruction, as in most obturating lesions of the small bowel, is not complete. Violent cramps, borborygmus, occasional attacks of vomiting and constipation are present. Visible peristalsis and intestinal erection are common. A palpable mass is practically always present in the lower right quadrant. In this phase of the disease fistulous communications with the colon or sigmoid may lead to the signs and symptoms of colitis, and mask the true nature of the disease. Occasionally the stenotic phase occurs as a primary manifestation of the disease; again, the symptoms may have been present for years (four years in one of our cases).

4. *Persistent Fistulas.*—Even before we had had a resected specimen to confirm our suspicion, we felt that a certain number of the persistent and intractable intestinal fistulas which followed on the drainage of a supposedly appendiceal abscess were in reality due to a nonspecific inflammatory disease involving the terminal ileum. This belief was founded on the following observations: 1. In a number of instances at the time of the second or third operation for closure of the fistulas, the appendix was found intact and not diseased. 2. Removal of the specimens from the sinus tract and from the intestinal end of the fistula failed to reveal any evidence of tuberculosis or other specific disease. 3. The occurrence of ileal without cecal origin of the sinus tract was noted. 4. The tendency of fecal fistulas of simple appendiceal origin is to close spontaneously or to be susceptible of closure by excision of the tract and inversion of the stump. However, in two instances resection of the intestine and fistulous tract revealed the typical pathologic picture of ileitis. We assume, therefore, that fistulas which are of supposedly appendiceal origin, but which have ileal openings and which have resisted simple surgical closure are, in the absence of tuberculosis, to be considered as cases of regional ileitis. One peculiar feature of these fistulas may be remarked: They may develop a few months after the original drainage operation, the wound meanwhile having healed and having remained healed for a few months. An abscess then develops in the wound; when this abscess mass is investigated, a communication with the intestine may be demonstrated.

ROENTGENOGRAPHIC OBSERVATIONS

Two outstanding facts, one negative and the other positive, are regularly noted. Since the disease simulates regularly the clinical characteristics of ulcerative colitis, the barium enema is first attempted. This procedure results in a negative report. The reason for this is evident in the light of the pathology of the disease. The colon is uniformly free from changes, even though the ileocecal valve is the seat of greatest intensity of the process.

The barium meal, however, when carefully interpreted, gives definite positive findings. These usually consist of distended loops of terminal ileum, in which a fluid level is discernible, and a definite delay in motility of the meal through the distal end of the small intestine. In the four, six and nine hour observations this delayed motility is usually present, though only in the late or stenotic stages is the delay striking. The milder degrees of stasis and puddling in the ileal loops may easily be overlooked by any but a careful roentgenologist. Even when the condition is plainly indicated, the true significance of these reported results may be glossed over by the clinician and an exact diagnosis may thus be missed.

When the ascending colon is the seat of a fistulous communication with the ileum, one may note some stricture deformity of the ascending colon or hepatic flexure, with delayed motility at this point. When the sigmoid is similarly involved in a fistulous tract, a true narrowing and delay at this flexure may simulate carcinoma and so create the necessary indication for operation. Both these areas of stenotic deformity of the large bowel are incidental to only one of the complications of the disease, namely, the formation of fistulous tracts. The entire colon is otherwise exonerated as a primary site of the granulomatous inflammation.

DIFFERENTIAL DIAGNOSIS

Regional ileitis must be differentiated from several analogous conditions which produce a

mass in the right iliac region with diarrhea and fever. The most important differentiation is that of regional ileitis from non-specific ulcerative colitis. The sigmoidoscopy and the barium enema suffice for the recognition of colitis in the largest percentage of cases. But there are types of colitis which involve only the proximal segments of the colon, and in which the sigmoid and the rectum are free from pathologic changes. While these instances are few and relatively uncommon, they do occur and lead to much confusion; they may be recognized by the deformity and spasm of the cecum and ascending colon when the latter areas are the seat of the segmental phenomena of colitis. Only in severe cases of ulcerative colitis does the process involve the terminal ileum, and then only for a few inches. In regional ileitis, all of the damaged tissue is proximal to the valve. The diagnosis is purely roentgenographic, the clinical differentiation being impossible. Colitis does not cause fistulas except about the anus and rectum; a mass is rarely palpable in colitis.

Ileocecal tuberculosis as a primary process should be easy of differentiation from regional ileitis. We are inclined, however, to agree with Moschcowitz and Wilensky[2] in the skepticism with which they view the actual occurrence of a primary tuberculous process at the ileocecal junction. To repeat their arguments, the latter disease must be rare, for only three cases have been seen at Mount Sinai Hospital in several years. Pathologic examination of all such suspected tuberculous masses has uniformly failed in the demonstration of tubercles or of tubercle bacilli in the sections or smears. Practically all cases mistakenly suspected of, or diagnosed as, ileocecal tuberculosis have been eventually classed as new growth, as appendicitis with abscess or as benign nonspecific granuloma. In all of our first cases of regional ileitis the diagnosis of ileocecal tuberculosis was the unvarying best possibility; operation was undertaken only after the customarily accepted methods of treatment for tuberculosis had been exhausted.

Fibroplastic appendicitis or typhlitis is a disease better known to the surgeons.

Lymphosarcoma, intestinal or mesenteric tuberculosis and Hodgkin's disease simulate regional ileitis in many of its features. The exact differentiation is possible only at the operating table or by the examination of pathologic specimens. Sarcoma of the intestine is usually multiple, causing dilatations at various levels, and involves the jejunum as well as the ileum and not particularly just the terminal 8 to 12 inches of the small intestine. Hodgkin's disease may give its characteristic monocytic blood picture, or a regional lymph node may reveal the true nature of the process.

Actinomycosis of the ileocecal region with fistula formation to the external abdominal wall must always be mentioned in the differentiation from ileitis. The extreme rarity of actinomycosis in this region of the body and in this climate makes this differentiation more theoretical than necessary.

From carcinoma of the terminal ileum or of the ileocecal valve the differentiation cannot be made with any certainty; both conditions call for surgical intervention and both lead to cure by successful and early resections.

TREATMENT

Medical treatment is purely palliative and supportive. The diseased area cannot be reached by colonic irrigations or enemas, and any attempts by medical means to reach a necrotizing, ulcerating and stenosing inflammation of the terminal ileum is purely and essentially futile. True, one case, discovered in the course of a cholecystectomy for stones, progressed to spontaneous healing or at least to a cessation of the intestinal symptoms.

But in general, the proper approach to a complete cure is by surgical resection of the diseased segment of the small intestine and of the ileocecal valve with its contiguous cecum. The restitution to complete health in thirteen out of fourteen cases as a result of the radical resection of the pathologic process or of a short-circuiting operation speaks vehemently in favor of surgical methods as the logical successful therapeutic procedure.

In one instance recurrent symptoms were accounted for by the finding of an annular stenosis a short distance proximal to the new anastomosis (ileotransversostomy). Apparently in this case the resection had not been carried out sufficiently oral to the lesion completely to eradicate the disease.

Our experience with short-circuiting anastomoses is limited. In one case a short-circuit ileocolostomy was performed through a segment of ileum that was apparently normal at the time

of operation. The pathologic process did not heal; on the contrary, the disease progressed to the proximal loop of the anastomosis. In two cases of intractable fistulas and in one case of inflammatory pelvic mass, ileocolostomy with exclusion has given excellent results. The best operation, as devised by Dr. A. A. Berg, consists of dividing the ileum 3 feet (91 cm.) from the ileocecal junction, closing both ends of the divided ileum and implanting the proximal terminus of the ileum by a side-to-side anastomosis at the transverse colon.

A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis)*

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In a paper upon renal lesions in endocarditis read before this Association in 1931, 17 cases were included which presented unusual vascular changes in the kidneys and other viscera. Most, but not all of the group had skin manifestations characteristic of disseminated lupus erythematosus. Although the pathogenesis of this group is still obscure, and several conditions may, therefore, be included, all the cases have something in common in their clinical course and pathological findings which justify their joint consideration. In the present report we propose to limit ourselves to a consideration of those cases which present the complete clinical picture, including the skin lesions.

This report is, therefore, confined to 23 cases of disseminated lupus erythematosus which died and came to necropsy. It must be emphasized, however, that a similar clinical picture and somewhat similar vascular lesions in the kidneys and other viscera were observed in cases without lupus.

Since the original descriptions of Hebra, Casenave and Kaposi, about the middle of the nineteenth century, the term lupus erythematodes or erythematosus has been applied by dermatologists to various erythematous lesions which appear on the face and tend to assume a butterfly pattern across the bridge of the nose and the malar eminences. In addition to the so-called acute or disseminated form, the term erythematous lupus is also used for a chronic indolent type of skin lesion which is discoid in appearance, is scaly, shows a tendency to hyperkeratosis when the scales are removed, and which may go on to atrophy of skin areas. It has also been employed for pellagra-like erythemas of the face and hands in persons whose skin exhibits an essential photosensitivity.

Patients with the chronic discoid lesions are otherwise not ill and, in our experience, do not die of the disease. Dermatologists report that they have sometimes observed the chronic discoid lupus and the more acute disseminated form at different times in the same individual. The group which we have studied includes every patient who died in our hospital with diagnosis of lupus erythematosus. None of them had ever had chronic discoid or atrophic lesions. A follow-up of other patients with acute ery-

* Reprinted from *Tr. A. Am. Physicians*, 50: 139–152, 1935, with permission of the publishers. To conserve space it has been necessary to omit the illustrations (of "wire loop" lesions in the kidney and other visceral lesions) and minor sections of the text.

Libman's description of an abacterial form of coarse verrucous endocarditis associated with disseminated lupus erythematosus (Libman, E. and Sacks, B. A hitherto undescribed form of valvular and mural endocarditis. *Arch. Int. Med.*, 33: 700–737, 1924) and Gross's basic cytologic observations in these cases (Gross, L. The heart in atypical verrucous endocarditis (Libman-Sacks). Emanuel Libman Anniversary Volumes 2: 527–550, 1932. International Press, New York City) stimulated an abiding special interest in disseminated lupus erythematosus at The Mount Sinai Hospital. The present study reflects an important phase in the development of this interest. Later contributions include Klemperer's studies of the fundamental pathology of the disorder (Klemperer, P., Pollack, A. D. and Baehr, G. Pathology of disseminated lupus erythematosus. *Arch. Path.*, 32: 569–631, 1941), which led to the concept of the "collagen" diseases, and the long-term observations on the suppressive effects of ACTH and cortisone by Baehr and Soffer.

A. B. G.

thematous lupus who were discharged from the hospital during a remission of the disease has revealed that most of them have since died of the disease.

The inclusion of several different conditions under the diagnosis of erythematous lupus upon the basis of superficial similarities in color or skin distribution has made for confusion. We are, therefore, confining our report to those cases which are associated with a grave constitutional illness and may go on to a fatal termination.

Clinical Picture. The clinical course is characterized by a more or less prolonged, irregular fever with a tendency to remissions of variable duration (weeks, months or even several years), by involvement of synovial and serous membranes (arthritis, pericarditis, pleuritis), by depression of bone-marrow function (leukopenia, thrombopenia, anemia) and by clinical evidences of vascular alterations in the skin, the kidneys and the other viscera. The disease often ends fatally after a period varying from four weeks to five years. One of the most remarkable characteristics of the disease is its sex linkage. Twenty-two of our 23 cases were females, 18 in the second or third decade of life; all were between puberty and the menopause.

At the onset, or else sometime later during the illness, the vascular lesions become visible on the skin as erythematous macules or patches which tend to become confluent. On the face the erythema assumes a characteristic butterfly pattern extending across the bridge of the nose and on the cheeks. It may also be present on other areas of the face and neck which are especially exposed to sunlight, the superciliary prominences, the upper lip, the prominence of the chin, the V-shaped exposed area of the upper chest and back. The erythema is also characteristically located on the ends of the fingers, around the nail-beds, on the thenar and hypothenar eminences, occasionally on the ends of the toes and the ball of the foot. Later, other areas of skin which are subject to rubbing or other mechanical trauma may become erythematous—the elbows and knees, the shoulders, the malleoli, the buttocks, the dorsal aspect of the forearms.

Small purpuric or petechial hemorrhages are often seen in the erythematous patches, especially on the hands. When the erythema has existed for some time, the area may show telangiectases, as evidences of more permanent vascular changes. A purplish blush is sometimes seen in intensely erythematous areas, especially on the face, elbows and chest, due to diffuse extravasations of red cells. Pigmentations may, therefore, persist in previously affected sites.

In some instances, there is a history that intense exposure to the sun immediately preceded the onset of the disease or of an exacerbation. Other patients had been mildly ill for weeks or months with low-grade fever and migrating arthritis. During convalescence from this illness they exposed themselves to sunlight. The severe sunburn was followed by a much severer recurrence of the illness. Thereafter the rash persisted, fever continued and the characteristic features of the disease became more evident. In other cases, no history of exposure to intense sunlight was given.

At the height of the disease, the patients often show erythematous or petechial areas on the mucous membrane, especially of the mouth. These soon develop into shallow ulcers surrounded by an erythematous or hemorrhagic areola. They tend to heal as the condition improves.

Perhaps, due to toxic damage to bone-marrow, or to vascular lesions in the marrow, the blood picture usually reveals evidences of a depression in bone-marrow function, leukopenia, thrombopenia and a moderate anemia (Dameshek). In the terminal stage of the disease, leukopenia may be succeeded by leukocytosis, especially if a terminal bronchopneumonia supervenes. In patients in whom the symptomatic purpura happens to be marked, hemorrhagic lesions may develop on the skin and mucous membranes.

Symptoms due to synovial membrane involvement occurred in 17 of the cases. At various times during febrile periods of the disease, sometimes before the appearance of the rash, most patients complained of arthralgia. The joint pains were usually mild and evanescent. In some instances they were accompanied by appreciable effusions into or around the affected joints. In 2 cases there were moderate deformities of phalangeal and other joints with permanent limitation of motion.

Clinical evidences of involvement of serous membranes were exceedingly common, usually symptoms and signs of pericarditis or of pleurisy. Heart murmurs were heard at some time during the disease in most cases, but not in all. A soft blowing systolic murmur at the apex was most

common. When heard, it was difficult to interpret its significance in the presence of pyrexia, anemia and a prolonged debilitating illness. In diagnosing the possible presence of endocarditis, the finding of petechiæ, even of white-centered petechiæ was also of little help, for they are too common, due to widespread alterations in the finer bloodvessels of the skin, mucous membranes and scleræ.

Dilatation of the heart's chambers was observed clinically and roentgenologically in advanced stages of the disease, sometimes with signs of passive congestion at the bases of the lungs. But symptoms of heart failure were usually absent except as part of the terminal picture. In 4 cases in which the involvement of vessels in the lesser circulation proved to be unusually extensive, the right side of the heart was especially enlarged. Three of these patients died after a terminal picture of right heart failure.

A variety of minor abnormalities in the electrocardiograms were encountered. The only abnormality characteristic of all electrocardiograms was low voltage, which was interpreted as evidence of the toxic damage to the cardiac musculature.

Aside from the skin and mucous membrane manifestations, the progressive injury to the peripheral vascular system in most cases ultimately resulted in clinical evidences of renal damage. Albuminuria and microscopic hematuria were usually observed and, when marked, gave rise to a suspicion of glomerulonephritis. In some instances this was supported by a tendency to fixation of specific gravity of the urine and sometimes in the last weeks of the disease by azothemia. The clinical evidences of renal injury were so characteristic that they were often of material assistance in establishing a diagnosis and in visualizing the extent of the systemic vascular injury.

Unlike in other systemic vascular diseases, such as periarteritis nodosa and malignant sclerosis, the blood-pressure usually remains normal. Only in 3 cases was a persistent moderate elevation above normal observed. Moderate edema of face and extremities occurred in a few instances, usually in a late stage, and was due essentially to the vascular injury in the skin. In 2 cases edema was caused by hypoproteinemia resulting from prolonged albuminuria and hematuria.

When viewed with the capillary microscope, the involved skin around the nail-bed of the fingers was seen to contain many more patent and dilated capillaries than normally. They were visible through a hazy film, due to the serum and red cells which had extravasated into the subcutaneous tissue. In some cases the exudation into the skin may be sufficient to lift the corium and form small blebs.

Ophthalmoscopic examination revealed fundus changes in 12 cases—perivascular hemorrhages, sometimes fluffy exudates and in 2 instances circumpapillary edema. The blood-pressure was normal in all but 1 of the 12 cases, so that the lesions may be interpreted as due to the essential vascular changes in the retina. The spleen was usually not appreciably enlarged. It was palpable only in 4 cases.

Pathological Findings. The serous membranes were found to have been involved in 17 of the 23 cases. A pericarditis, sometimes adhesive, was most common, being present in 12 cases, in 10 of which it was associated with evidences of a pleuritis. The pleura was involved

Table 1

CLINICAL SUMMARY OF 23 CASES OF LUPUS ERYTHEMATOSUS

Sex—female, 22; male, 1.		Age—10 to 20 yrs.	9		
		21 to 30 "	9		
			—	18	
		31 to 40 "	4		
Duration—5 wks. to 4½ yrs.		Over 40 "	1		
			—	5	
Butterfly facial le ion	22	Arthritis			17
Erythema	22	Serous membranes			17
Mouth lesions	14	Pericarditis and pleuritis		10	
Purpura or petechiæ	11	Pericarditis only		2	
Fundus lesions	9	Pleuritis only		5	
Palpable spleen	4				

Depression of hematopoiesis:			
Hemoglobin	38 to 76%	20 out o	20
Red blood cells	2 to 3.8 MM.	12 out of	13
Leukopenia	4 to 6 M.	9 out of	23
Thrombopenia	70 to 190 M.	9 out of	12
Albuminuria			23
Microscopic hematuria			19
Azothemia, moderate			7
Azothemia, marked			2
Hypertension, moderate			3

Table 2

PATHOLOGICAL FINDINGS IN 23 CASES OF LUPUS ERYTHEMATOSUS

Visceral vascular lesions	20
Glomerular lesions in 18.	
"Wire loop" lesions in 13.	
Vascular lesions limited to skin and eye	1
Skin only	2
Coarse verrucous endocarditis (nonrheumatic)	13
Type Libman-Sacks, 5.	
Nonrheumatic verrucæ, 8.	
No endocarditis	9
Unknown (heart lost)	1
Aschoff bodies in myocardium (22 cases)	0

alone in 5 instances. A terminal bronchopneumonia was often present.

Evidences of active tuberculosis were absent in all but two cases. One had a single caseous tracheo-bronchial lymph node. Another, who had suffered from this debilitating illness for more than a year, was found to have a terminal acute general miliary tuberculosis. The absence of tuberculosis in 21 cases seems more significant.

A coarse verrucous form of endocarditis was found upon the mitral or tricuspid valves in 13 of the 23 cases. In 5 of these, the valvular vegetations were extensive and extended on to the chordæ tendinæ and the endocardium of the ventricle. The endocarditis in these 5 cases conformed exactly to the type described in 4 cases by Libman and Sacks before this Association, in 1924, as indeterminate endocarditis. Two of their patients had lupus erythematosus. In 8 other cases in our series, smaller verrucæ were present on the mitral or tricuspid valves, which were coarser and otherwise different from the verrucæ of rheumatic endocarditis. Attention has long been directed by Libman to this atypical variety of endocarditis which is not due to rheumatic fever nor to any of the known bacteria. The histology of these endocardial lesions will be reported by Gross and Friedberg. In 2 of our cases the mitral cusps presented deformities characteristic of old rheumatic valvular disease.

In 9 of our lupus cases, no endocarditis whatever was found. In 22 hearts which were studied histologically with great care, no Aschoff bodies were found. The unanimity of these observations would eliminate the possibility that active rheumatic fever might have played a rôle in producing the endocarditis or the vascular lesions.

In 2 cases the surface of the kidneys was studded with irregular depressions. These were due to multiple vascular occlusions and resembled in some respects the surface appearance of the kidneys in so-called malignant arteriosclerosis. Anemic infarcts were twice observed in the spleen and in the kidneys and several cases showed emboli within pulmonary arteries.

The microscopic examination usually revealed remarkable vascular lesions in the finer ramifications of the systemic and sometimes also the pulmonary circulation. In the kidneys conspicuous vascular alterations were found in 20 cases. In the other organs (myocardium, lung, liver, pancreas, spleen, ovaries) the incidence of vessel changes was not as high. In 6 cases the vascular lesions were widespread in all the viscera. The vessels of the lesser circulation were conspicuously involved in 4 cases. The skin showed similar alterations in all instances in which material was obtained.

Histologically, the vessel lesions represent a variety of changes:

1. Simple dilatation of capillary beds in certain areas, as in the skin, with blood and serous extravasations.

2. Proliferative lesions of the lining endothelium of capillaries, arterioles and venules, associated with thrombi which often obstructed or occluded the lumen.

3. Degenerative and necrotizing lesions in the wall of such vessels, associated with thrombosis and sometimes with hemorrhage into the adjacent tissues. The severer lesions were especially conspicuous in the capillaries and arterioles of the kidney.

Because all three types were often found in the same case, they may be considered as stages of the same underlying morbid process. Isolated vascular lesions of similar appearance may at times be encountered in a careful histological study of persons who have died of any acute or chronic infectious process (Siegmund). Our group of cases is distinguished by the systemic distribution of the vascular lesions in various viscera.

Glomerular changes were especially conspicuous in 18 of the cases. Proliferative and thrombotic lesions of glomerular loops were frequent. In 2 cases the glomerular changes were sufficiently extensive to be called a true diffuse glomerulonephritis. In 3 instances the proliferative and necrotic process involved only segments of glomeruli, thereby creating a superficial resemblance to the embolic glomerular lesions of subacute bacterial endocarditis. Unlike true embolic lesions, the remaining non-necrotic segment of the affected glomeruli was not normal. In 5 cases no glomerular changes were observed.

The commonest and most characteristic glomerular alteration was a peculiar hyaline thickening of the capillary walls which is striking even in sections stained with hematoxylin eosin. The thickened wall appears rigid, as if made of heavy wire. We have, therefore, called it the "wire loop lesion." It was present in 13 cases. No special staining is required, although it usually stains red or reddish-blue with Mallory's

stain. The greatly thickened "wire loops" of the affected glomeruli contain no amyloid or lipoid material. Some may contain a little fibrin. This very characteristic lesion has not been seen by us in any other human disease, except perhaps in eclampsia. It resembles the glomerular and vascular lesions described by Wadsworth in horses which have been immunized by repeated intravenous injections of live bacteria, especially of the pneumococcus-streptococcus group. It is quite different from the hyaline degeneration seen in glomeruli of arteriosclerotic kidneys or of chronic glomerulonephritis. It apparently represents a toxic degenerative process.

Bacteriological Observations. Thirty-six blood cultures taken upon 20 of the patients during febrile periods of the disease were negative. The bacteriological flora of the nose and throat was studied qualitatively and quantitatively. No one organism was regularly present or regularly predominant.

Common colds and other acute infections of the upper respiratory tract often precipitated an exacerbation of the illness. Yet it could not be concluded that these upper respiratory infections had any direct relationship to the persistence of subsequent symptoms.

In spite of these inconclusive bacteriological observations, it seemed clinically as if the patients were suffering from a peculiar constitutional reaction to a low-grade infection. The variety or intensity of the local infection was apparently not important. The severity of the constitutional reaction to this obscure intoxication seemed to depend rather upon some peculiarity in the reaction of the individual.

Significance of the Skin Lesions. Although the rash of lupus erythematosus is due to vascular changes similar to those which develop in the viscera, the onset and persistence of the skin lesions seems clinically to bear some relationship to the subsequent development of the visceral alterations and of the constitutional manifestations. Although in some instances the skin lesions appeared without any direct exposure to intense sunlight, in others it was initiated by a definite sunburn and then persisted, often with repeated remissions and exacerbations. It should be emphasized that none of our patients has previously shown any evidences of photosensitivity. Two of the patients seemed well before they exposed themselves to the sun. Five others had been ill for some time with an obscure irregular fever of moderate intensity, malaise and migrating arthritis, but without a rash. During convalescence from this illness they exposed themselves for some time to bright sunlight in the country, at the seashore or on a boat. What seemed then to be a bad sunburn persisted thereafter as an intense erythema on the cheeks, bridge of the nose, superciliary regions, upper lip, chin and exposed area of the chest. Fever, weakness and all the clinical manifestations of the original disease, became greatly intensified. Gradually, clinical evidences developed of progressive vascular alterations in the viscera and especially the kidneys, and the patients became progressively sicker.

Although the skin of our patients had not been unusually photosensitive before the appearance of the lupus, a search of the blood and urine for various porphyrins was made in 2 cases by Dr. C. K. Friedberg, but none was found. After the appearance of the skin lesions and the subsequent intensification of all the systemic and vascular manifestations, the finer vessels of the skin become more sensitive to all types of trauma. Petechiæ sometimes appear in the antecubital space when the veins of the upper arm were obstructed with a tourniquet. Erythemas may develop on parts of the body subjected to rubbing or other mechanical trauma—the elbows, knees, shoulders, dorsum of the extremities. These areas of erythema sometimes become petechial or purpuric.

In spite of the fact that they often seem to play a sensitizing rôle, probably neither sunburn nor the facial lesions of lupus are absolutely essential. This is indicated by the following observations:

1. The other clinical and visceral manifestations sometimes precede the onset of the skin lesions or the sun exposure.

2. One of our cases, a rather dark-complexioned Puerto Rican woman, developed no facial rash, although the skin lesions on the hands were recognized by all dermatologists who saw her as absolutely typical of lupus erythematosus. The rest of the clinical picture (fever, arthritis, leukopenia, pericarditis) was identical with our other cases and the vascular lesions in the viscera proved to be most marked and widespread.

3. Most of our cases had periods of the disease when the skin lesions disappeared, although other clinical evidences of the illness persisted.

4. In a few instances we have observed a prolonged irregular fever, involvement of synovial and of serous membranes, renal damage, depression of bone-marrow function and all

other clinical manifestations in individuals who did not develop lupus at any stage of the disease and who showed at necropsy diffuse vascular as well as endocardial changes similar to those observed in our lupus cases.

PATHOGENESIS. Some of our patients had been previously treated with injections of gold chloride. We believe that the treatment was of no value. Remissions occur spontaneously after any form of therapy. In some instances it was suspected that the patient may have been made worse by the treatment. In a disease in which severe renal vascular damage occurs so frequently, this nephrotoxic salt seems contraindicated. There is also reason to believe that the gold chloride may have accentuated the depression of hemapoiesis. That injections of gold chloride were not the cause of the vascular lesions in the viscera was obvious, for many cases which showed the severest vascular alterations at necropsy had not received this treatment.

Because of the widespread bloodvessel lesions and the tendency to purpuric phenomena in some cases, it was necessary to consider the possible rôle of a vitamin deficiency, especially vitamins C and G. The patients had eaten adequate amounts of meat, so that the latter could be eliminated. In 2 instances the patients had been living upon a diet from which citrus fruits and tomatoes had been excluded since shortly after the onset of the disease. In neither case did the administration by mouth of large amounts of vitamin C containing foods, nor the daily injection of cevitamic acid result in any clinical improvement. In 3 of our cases, Dr. Philip Finkle found a remarkably low rate of excretion of cevitamic acid even after saturation of the patients with liberal amounts of vitamin C containing foods. Similar observations were made in cases of thrombopenic purpura. It is too early to state whether the diminished excretion of the cevitamic acid may not be a result rather than a cause, secondary perhaps to the extensive vascular injuries and the exudation and hemorrhage into the tissues.

A discussion of the possible pathogenesis of this condition would not be complete without consideration of the remarkable sex linkage of the disease and its age incidence. The only male among our 23 cases was a rather doubtful case who died within four weeks after the onset with suppurating lymph nodes of the neck and a bronchopneumonia. No vessel changes were found in any of the viscera and there was no endocarditis. The case is included because the erythema of the face was diagnosed by dermatologists as lupus erythematosus, although it was atypical.

Aside from the fact that 22 of our 23 cases were females, it seems significant that 18 were in the second and third decade of life and all 22 were between puberty and the menopause. No significant endocrine or menstrual disorder was observed. Nevertheless, the rôle of the normal ovarian functions must at least be considered as a possible contributing or predisposing factor, for certain cyclical variations in ovarian function are often associated with changes in the skin. They may also be associated at times with a tendency to bleed from mucous membranes and with other vascular phenomena in the skin and mucous membranes. Certainly, the sex and age incidence of this disease of the peripheral portions of the systemic and pulmonary circulations are so strikingly consistent that they must be significant.

The probable rôle of low-grade infections has already been discussed. It would seem that the disease is conditioned not by the nature or severity of the local infection but by a peculiarity in the constitutional reaction of the host. Whatever the exact nature of the intoxication, it exhibits its effect primarily upon endothelium-lined structures, capillaries, small arteries and veins, the endocardium and the synovial and serous membranes, the most conspicuous pathological changes occurring in the finer peripheral and visceral ramifications of the systemic and sometimes also the pulmonary circulation.

End of Text Commemorating Centennial of The Mount Sinai Hospital of New York.

Review

The Natural History of Cushing's Syndrome*

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APPROXIMATELY two decades have passed since Cushing[1] first drew attention to the clinical syndrome which now bears his name. Whether Cushing's syndrome is initiated by a pituitary,[1,2] adrenal[3-7] or hypothalamic[8] lesion remains a matter of controversy; however, it is generally agreed that the clinical picture it presents is that of hyperadrenalism. The disease has always been one which attracted the attention of endocrinologists but recently the similarity between this entity and hyperadrenal states induced by the administration of adrenocorticotrophic hormone (ACTH) or cortisone has awakened a more general interest.

It seems timely, therefore, to report thirty-three cases of Cushing's syndrome collected from the Neurological Institute and the medical and urologic services of the Columbia-Presbyterian Medical Center and to review 189 cases collected from the literature. It is hoped that the resulting information will summarize the natural history of the spontaneously occurring disease, furnish a basis of comparison with induced hyperadrenalism and perhaps elucidate the problems arising in long-term hormonal therapy.

METHOD OF STUDY

The thirty-three patients with Cushing's syndrome who comprise the present series were collected from the records of the Columbia-Presbyterian Medical Center during the years 1932 to 1951.† Reports of an additional 189 patients from the literature were reviewed to furnish an adequate cross section of the disease picture.[1,2,5,7,11-132] It has been the intention of the present reviewers to limit the cases selected to those patients in whom the syndrome was manifested in full clinically[133,134] and, when possible, documented by laboratory and histologic study. The thirty-three Columbia cases all exhibited the classical physical characteristics of Cushing's syndrome on inspection and showed at least three of the five commonly encountered abnormalities, i.e., hypertension, purple striae, menstrual disturbances or impotence, osteoporosis and a diabetic glucose tolerance curve. Comparison has been made, when indicated, with the additional group of 189 cases.

Age, Sex and Duration of Disease. In the Columbia series there were twenty-seven females and six males, but the preponderance of females over males in the entire series was only three to one. Two patients in the present series were Negroes, and only one other Negro[95] was encountered in the group of 189, giving an over-all incidence of only 1.3 per cent. The average age at onset of the disease in patients in the present (Columbia) series was thirty-one, with an age range of eleven to fifty-five years. One of the thirty-three patients in the present series has been lost to follow-up. Of the remaining thirty-two patients, seventeen died after an average of four and one-half years of known disease and fifteen remain alive, having had their disease an average of nine years. It appears then that approximately half of the patients with Cushing's syndrome will die within five years.

Symptoms and Signs (*Table* 1). Obesity was the most common finding and it was peculiarly distributed over the face, neck and trunk, giving rise to the classical "moon" facies, "buffalo hump" and "truncal" obesity, sparing the extremities. Cushing originally described painful adiposity[1] but pain or tenderness of fatty tissue was uncommon in the present series. Obesity was frequently the first symptom to appear. In several instances "pseudo-obesity" was a more accurate term in that no change in total body

† Three of these patients, L. F., L. G. and E. G. have been reported previously.[9,10]

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weight occurred, while there was a marked alteration in distribution of fat and in facial appearance. The other major findings included hypertension (frequently with high diastolic readings), mild degrees of hirsutism (facial and lanugo-like body hair being prominent), acne,

TABLE I
SYMPTOMS AND SIGNS IN PATIENTS WITH CUSHING'S SYNDROME

Symptoms or Signs	Columbia Series Per cent (33 Cases)	Previously Reported Per cent (189 Cases)
Obesity	97	97
Hirsutism	73	69
Hypertension	84	85
Amenorrhea, Oligomenorrhea, Impotence in men	86	71
Plethoric appearance	89	50
Purple striae	60	71
Mental symptoms (major 24%) (minor 43%)	67	31
Poor wound healing or severe infection	42	30
Weakness and backache	83	50
Acne, skin pigmentation or other rash	82	26
Purpura or easy bruisability	60	23
Ankle edema	60	28
Headache	58	34
Neurologic symptoms or signs	39	17
Polydipsia or polyuria	39	25
Virilism	9	5
Exophthalmos	6	8

menstrual disturbances (or impotence in men) and the peculiar purple striae which are uncommon in uncomplicated obesity. Cardiac enlargement occurred with prolonged hypertension.

Mental symptoms ranging in severity from irritability and depression to major psychosis occurred in two-thirds of the patients in the present series whereas they were reported in only one-third of the cases garnered from the literature. The mental illnesses included hysteria, suicidal depressive states, simple schizophrenia and paranoia. Even in the absence of major psychiatric disturbances these patients usually presented a difficult problem in management because of emotional lability.

Headache, when it occurred, did not follow any particular pattern and was not regularly correlated with the presence of pituitary neoplasm. Weakness and backache were generally associated with osteoporosis. A plethoric appearance, when noted, was not closely correlated with the presence of polycythemia.

Neurologic symptoms and signs occurred in 39 per cent of our series (19 per cent in cases from the literature). Muscular weakness and tremor were the most commonly noted abnormalities but symptoms ranging from minor visual disturbances to hemiplegia were encountered. Occasionally these were associated with a pituitary tumor.

Poor healing of wounds or unusual failure to localize minor infection was noted in the history in 42 per cent of the present group and in 33 per cent of those from the literature.

Laboratory Findings (*Table* II). Because of the discrepancies encountered in comparing laboratory data from many institutions, the present series alone will be described. Despite the emphasis in Cushing's original report on polycythemia,[1] in over half of the cases in the present series red blood cell counts were within normal limits. The highest count encountered was one of 6.9 million (H. Hu.). The eosinophil count, as determined either directly or calculated from the total count and differential smear, was below 100/mm.^{3} in 79 per cent of the cases. Despite the frequency of marked osteoporosis and occasionally increased calcium excretion in the urine,[135] calcium, phosphorus and phosphatase levels were consistently within normal limits. The highest serum alkaline phosphatase level was 5.6 Bodansky units. Ninety-four per cent of the cases exhibited distinctly diabetic glucose tolerance curves. However, in less than a fourth of the patients was glycosuria present and only five had frank diabetes. Hence, it appears that while carbohydrate tolerance is consistently decreased, severe diabetes is unusual. In a third of the cases polydipsia or polyuria occurred, for the most part unrelated to the presence of glycosuria.[136] Despite the high incidence of atherosclerosis in patients with Cushing's syndrome, the serum cholesterol exceeded 250 mg. per cent in only 39 per cent of the patients. There was no significant hypoalbuminemia or hyperglobulinemia. In most instances the erythrocyte sedimentation rate and hematocrit were normal.

In twenty-five patients of the Columbia series the twenty-four-hour excretion of 17-ketosteroids in the urine was determined. The average value

was 12.2 mg./twenty-four hours with a range of 0 (in one patient, L. G., with a benign adenoma) to 26.6 mg. (patient S. G. with presumed bilateral adrenal hyperplasia). The very high levels found in the adrenogenital syndrome were not encountered. The mean level of six patients who were found at operation or autopsy to have a unilateral benign adrenal adenoma was 4.8 mg./twenty-four hours. The average of eleven patients subsequently proved to have adrenal cortical hyperplasia was 15.1 mg./twenty-four hours. While the number of cases is small, there is little overlap and it is possible that adrenal cortical hyperplasia leads to higher excretion of 17-ketosteroids than does adrenal cortical adenoma. However, these results are based, for the most part, on single determinations and, with the known daily fluctuations in the excretion of 17-ketosteroids, this finding requires further confirmation. In the one patient of the present series with an adrenal carcinoma, (L. F.), the 17-ketosteroid excretion was not determined. It might be expected that the highest levels would be encountered in this group, since such patients not infrequently exhibit certain features of the adrenogenital as well as the Cushing syndrome. In seven of the patients the excretion of "corticoids" (so-called 11-oxysteroids) was determined chemically, either by the phosphomolybdic acid or the formaldehydogenic method. It was found to range from 0.86 to 7.11 mg./twenty-four hours. In six of the seven it was in excess of normal. In one patient, C. T., a boy of seventeen years, gynecomastia was noted and determination of his urinary estrogens revealed a markedly increased excretion.

TABLE II

LABORATORY DATA IN THIRTY-THREE PATIENTS WITH CUSHING'S SYNDROME (COLUMBIA SERIES)

		Range	Over-all Average
Red blood cell count	48% above 5.0 million/mm.³	3.4–6.9	5.02
White blood cell count	48% above 10,000/mm.³	5,800–15,000	10,050
Eosinophiles	79% below 100/mm.³		57
Basal metabolic rate (32 cases)	7% above +20 20% below −20	−37–+32	−6
24-hour uptake of radioactive iodine (5 cases)		8–51	24%
Fasting blood sugar	49% above 100 mg. %	61–300	116
Diabetic glucose tolerance (31 cases)	Present in 94%		
Frank diabetes	Present in 15%		
Serum calcium (28 cases)		9.0–11.3	10.0
Serum phosphorus (25 cases)		22–4.4	3.0
Cholesterol (28 cases)	39% above 250 mgm%	147–460	269
24-hour 17-ketosteroid excretion (25 cases)	20 females	0–20.0	10.8
	5 males	15.1–26.2	17.8
24-hour 11-oxysteroid excretion (6 cases)	Formaldehydogenic method (Normal 0.5–1.5)	0.86–6.3	3.87
(1 case)	Phosphomolybdic acid method (Normal 2–4)		5.02
Glycosuria	Present in 27%		
Albuminuria	Present in 50%		
Serum carbon dioxide content-mEq./L. (27 cases)		21.2–46.2	29.5
Serum chlorides-mEq./L. (27 cases)	37% below 100.0 mEq./L.	78.1–107.4	99.6
Serum sodium-mEq./L. (14 cases)		136.0–147.0	142.7
Serum potassium-mEq./L. (11 cases)		3.2–5.3	4.2

McQuarrie[85] and others[70,137] have noted abnormally high serum sodium and bicarbonate and low serum potassium and chloride values in patients with Cushing's syndrome. Only 37 per cent of the twenty-seven patients in the present group of patients in whom serum chloride levels were determined had values below 100 mEq./L.; however, the over-all average of all was 99.6 mEq./L. Sixty-four per cent had carbon dioxide combining powers above 28/0 mEq./L. and the average of all was slightly elevated at 29.2 mEq./L. One patient, G. O., had a carbon dioxide content of 46.2 mEq./L. with chlorides of 78.1 mEq./L. but extremes such as these were unusual. In fourteen patients

the serum sodium was determined, the results indicating an average value of 142.7 mEq./L. and a range of 136.0 to 147.0 mEq./L. Four patients had sodium levels over 145.0 mEq./L. The average of eleven potassium levels was 4.2 mEq./L., range 3.2 to 5.3 mEq./L. Hence,

TABLE III
X-RAY FINDINGS IN CUSHING'S SYNDROME
(THIRTY-THREE CASES)

	Per cent
Skull (30 cases):	
Decalcification	60
Deformed sella turcica	3
Spine (29 cases):	
Decalcification	83
Compression fracture	31
Rib fractures recorded	12
Airograms (26 cases):	
Suspicious for cortical adenoma	69
Normal	31

while some patients with Cushing's syndrome may show disturbances in the serum level of sodium and potassium, the majority of patients do not show any such abnormality.

The electroencephalogram was abnormal in four of eight patients examined. The findings in these four abnormal records were similar to the electroencephalographic abnormalities reported by Hoefer and Glaser[138] in patients receiving ACTH.

X-ray Findings (*Table* III). Osteoporosis or decalcification was the most common finding in roentgenograms, occurring in the spine in 83 per cent and in the skull in 60 per cent of the Columbia patients. Cushing originally reported osteoporosis in six of his twelve cases and Gamna and Forconi[139] and others have pointed out the frequency of this manifestation. Perirenal insufflation was performed in twenty-six patients. The results were considered suspicious for adrenal tumor in eighteen. Seventeen of these patients were explored and an adrenal tumor was found in five. One other patient had a tumor confirmed at autopsy. In eight instances the perirenal aerogram was considered negative for tumor and in none of the three patients in this category who were explored was a tumor found. Cahill[10] has stated that "in obese (patients) and especially in those with Cushing's syndrome, the air diffuses poorly because of the fatty edema in the perirenal tissues." However, this technic despite its limitations remains the only available method, apart from operation, of furnishing a clue to the existence and location of a small tumor, such as a small benign adenoma. The remainder of the x-ray studies showed nothing of significance.

Clinical Course (*Table* IV). Of the thirty-two patients in the Columbia series who have been followed continuously, seventeen were dead within an average of five years of onset of symptoms. The causes of death will be discussed later. The disease was progressively down-hill in those patients who succumbed. One patient, C. F., has been followed for over nineteen years and has had symptoms of Cushing's syndrome for over twenty years. She has shown improvement following pituitary irradiation but still maintains several stigmata—notably mental disturbances—of her disease. The most fulminating case in the series was also the youngest (A. G.). This eleven year old boy was first seen four months after onset of symptoms by which time he had characteristic obesity, plethora, headache, hypertension, polyuria, osteoporosis, striae and emotional lability. He failed to respond to medical treatment. After six months of observation an aerogram was reported suspicious for adrenal tumor. The left adrenal was not visualized and the right adrenal appeared normal on exploration. He died of severe postoperative wound infection ten months from the onset of his first symptom. Postmortem consent was not obtained in this case. The majority of patients have had courses between these two extremes. The fatal cases had, in general, progressive debility while those who have survived have had exacerbations and remissions occasionally coincident with therapy which will be discussed later.

A striking feature of the clinical course of patients in the present series is that seven of the nineteen patients who underwent an operation showed evidence of poor wound healing or marked inability to localize simple infection. Cushing,[1] Cahill,[140] Brunner[18,19] and others have remarked on the apparent increased susceptibility to infection of patients with Cushing's syndrome. McQuarrie's[85] patient died of streptococcal sepsis following tooth extraction. Four of Heinbecker's[8] six cases had miliary spread of tuberculosis or poor healing during the course of their Cushing's disease. Lawrence and Zimmerman,[76] Levi,[80] Hall et al.,[51] Radovici et al.,[107] and many others have reported cases which showed poor healing of skin infections. These findings are consistent with the observations of Ragan et al.[141] on the inhibitory effect of

TABLE IV

THERAPY, COURSE AND PRESENT STATUS OF THIRTY-THREE PATIENTS WITH CUSHING'S SYNDROME

Pt., Sex, Age	Follow-up (yr.)	Form of Therapy	Course	Present Status
S. K. M, 20	6 mo.	Subtotal unilateral adrenalectomy; pituitary irradiation	.....	Improved slightly
C. C. F, 27	8 mo.	Pituitary irradiation; (negative airograms)	Paranoid trends decreased; facial swelling and weight decreased	Improved temporarily
R. C. F, 30	2½	Bilateral partial adrenalectomy; pituitary irradiation	Developed psychosis postoperatively, institutionalized; complete remission 12–18 mo. later	In remission
R. W. M, 33	6½	Pituitary irradiation; testosterone; adrenal irradiation	Myocardial infarction and thrombophlebitis; improvement initially but recurrence and no improvement following 2nd course irradiation	Unimproved
B. C. F, 31	5½	Adrenal biopsy; Radon seed implantation *	Poor wound healing; gradual improvement after implantation	Improved
M. F. F, 17	6	Pituitary irradiation	Weight loss, resumption of menses	In remission
C. R. F. F, 24	19	Pituitary irradiation	Weight loss, facial hair less, resumption of menses; mental symptoms (hallucinations) persist	Improved
M. deT. F, 46	2½	Pituitary irradiation	Mental symptoms improved; developed congestive heart failure	Improved slightly
C. T. M, 17	3½	Airograms suspicious—no tumor found at operation; pituitary irradiation	Blood pressure diminished, disappearance of moon facies; mental symptoms persist	Improved
E. G. F, 30	6	.....	Became pregnant and had full-term stillbirth	Unimproved
D. W. F, 40	4	Pituitary and adrenal irradiation, methyl testosterone	Weight loss, blood pressure diminished, menses resumed; normal delivery subsequently	In remission
H. Hur. F, 27	4½	Bilateral subtotal adrenalectomy †	Clinical improvement followed subtotal adrenalectomy	Improved
G. S. F, 48	1½	.....	Problem of diabetic management	Improved
M. N. F, 30	8	Adrenal adenoma removed	Complete clinical improvement including clearing of depression followed removal of adenoma	In remission
H. P. F, 25	8	Pituitary irradiation; adrenal adenoma removed	Gradual improvement followed removal of adenoma, including improvement in mental symptoms; normal pregnancy and delivery subsequently	In remission
H. F. F, 38	3 mo.	.....	Became psychotic requiring institutionalization; developed erysipelas; died of cardiac decompensation	Dead 13 months after first symptom; autopsy ‡
A. D. F, 29	4	Pituitary irradiation	Poor wound healing; abnormal mentally; chronic ill health; died following subarachnoid hemorrhage	Dead 7 years after first symptom; autopsy
H. Hug. F, 26	2	.....	Continued ill health; died intestinal obstruction secondary to intussusception	Dead 9 years after first symptom; autopsy §

TABLE IV.—(*Continued*)

Pt., Sex, Age	Follow-up (yr.)	Form of Therapy	Course	Present Status
M. deG. F, 44	2 mo.	No adrenal tumor found at operation; pituitary irradiation	Abnormal mentally; died, subarachnoid hemorrhage shortly after pituitary irradiation	Dead 4 years after first symptom; autopsy**
L. M. F, 31	5½	.....	Cerebral vascular accident; died suddenly, 1 year later	Dead 6 years after first symptom; no autopsy
R. A. F, 37	3½	Pituitary irradiation	Chronic congestive heart failure and death	Dead 6 years after first symptom; autopsy††
G. O. F, 56	4 mo.	Pituitary irradiation	Gradual downhill course and death	Dead 2½ years after first symptom; autopsy
J. T. F, 24	6½	Pituitary irradiation	Recurrent infections; mental symptoms; died cerebral hemorrhage	Dead 8½ years after first symptom; no autopsy
R K. F, 28	3	Sympathectomy; teratoma removed (no adrenal tissue); partial resection 1 adrenal-(hyperplasia); pituitary irradiation	Had psychotic episodes requiring institutionalization; developed streptococcic sepsis, myocardial infarction, pulmonary infarctions, chronic cardiac failure	Dead 7 years after first symptom; autopsy
S. G. M, 29	3	Pituitary irradiation	No improvement; died of pneumonia	Dead 3½ years after first symptom; no autopsy
A. K. M, 20	1½	Pituitary irradiation; adrenals explored; hyperplasia	Psychotic, requiring institutionalization; died in pulmonary edema 11½ weeks postoperatively	Dead 2 years after first symptom; no autopsy
L. P. F, 29	1½	Adrenal tumor removed	Died postoperatively, abnormal mentally	Dead 4 years after first symptom; no autopsy
A. G. M, 11	6 mo.	No tumor found at exploration	Died; massive postoperative wound infection	Dead 10 months after first symptom; no autopsy
R. Wi. F, 26	4 mo.	No tumor found at operation (hyperplasia)	Cardiac and renal decompensation; acute psychosis requiring institutionalization	Dead 3½ years after first symptom; autopsy‡
L. F. F, 36	1	Carcinoma of adrenal removed	Temporary improvement, return of symptoms and death with metastases	Dead 3½ years after first symptom; no autopsy
L. G. F, 27	2 wk.	Adrenal adenoma removed	Abnormal mentally; died postoperatively	Dead 2½ years after first symptom; autopsy
J. R. F, 47	1 mo.	Adrenal adenoma removed	Died postoperatively	Dead 6 years after first symptom; no autopsy
E. Ga. F, 40	1	Airogram suspicious	Persistent mental symptoms	Lost to follow-up; unimproved when last seen

* Implanted by Dr. Davidoff at Montefiore Hospital, New York.
† Done at Mayo Clinic, Rochester, Minn.
‡ At Bellevue Hospital, New York.
§ At Lawrence Hospital, Bronxville, N. Y.
** At New Haven Hospital, New Haven, Conn.
†† At Barnett Memorial Hosp., Paterson, N. J.

iatrogenic hyperadrenalism on wound healing and localization of inflammation.

Psychosis or neurosis severe enough to require institutionalization occurred in eight of our thirty-three patients. It is difficult to evaluate this factor in reviewing the 189 additional case reports from the literature since many cases included only short periods of observation. Sanchez-Calvo[142] reported pituitary basophilism in seventeen of thirty-two mental patients but it is doubtful that they actually had Cushing's syndrome. Urban's[125] patient was depressed and committed suicide as did Case 3 of Mellgren.[88]

Two patients (R. K. and R. W.) have had

TABLE V

EFFECTS OF PITUITARY IRRADIATION IN CUSHING'S SYNDROME (EIGHTEEN PATIENTS)

Pt., Sex, Age	Tumor dose (Rɸ)	Date Therapy Started	Duration of Therapy (days)	Results
A. K. M, 21	2800†	Summer, 1944	.....	No improvement; died 12/4/44; pulmonary edema and shock, 3 months after last of two adrenal biopsies; no tumor found; no autopsy
R. A. F, 37	1050	June, 1943	13	No improvement; died 1946; autopsy:‡ basophilic hyperplasia; benign adenoma left adrenal cortex with atrophy right adrenal
A. D. F, 27	1100	June, 1933	12	No improvement; died 2/7/36; autopsy: basophilic adenoma, adrenal hyperplasia
	1400	Oct., 1933	17	
	1400	Mar., 1934	15	
J. T. F, 24	1200 } Total	May, 1939	13	No improvement; Sept. 1942 given 400 Rɸ (tumor dose) in 13 days to adrenals, no improvement; given methyl testosterone, no improvement
	1200 } 6750 Rɸ	July, 1939	10	
	1550 } in 11 mo.	Oct., 1939	16	
	1600 }	Jan., 1940	22	
	1200 }	Apr., 1940	17	
	1100	June, 1942	12	No improvement; died 2/18/46 at home of "cerebral hemorrhage;" no autopsy
R. K. F, 28	2550	July, 1949	33	No improvement; died 12/29/49; autopsy: cardiac failure, pulmonary infarcts, hyperplasia of adrenals, pituitary not examined
S. G. M, 29	1200	Nov., 1944	25	No improvement
	900	Oct., 1947	16	No improvement; died 11/19/47; pneumonitis; no autopsy; airograms Oct. 1947 showed bilaterally enlarged adrenals
H. P. F, 25	1350	Jan., 1944	15	No improvement; operation, May, 1944. 15 gm. right adrenal tumor removed; subsequently cured; normal pregnancy and delivery 1947
	1350	Apr., 1944	28	
G. O. F, 56	1000	Aug., 1944	8	No improvement; died 9/12/44; autopsy: pulmonary infarctions, Crooke's changes in pituitary, adrenal cortical hyperplasia
R. C. F, 30	1400	Sept., 1949	16	No improvement within a year; bilateral adrenal biopsy June–July 1949; no adrenal tumor found; psychotic July, 1949; complete remission late 1950, following a course of electroshock treatments
M. deT. F, 46	2275	Aug., 1949	36	No improvement; patients still under observation; adrenal airograms: no evidence of tumor
	2250	June, 1950	36	
M. deG. F, 44	1800	Dec., 1945	.....	Temporary improvement; mental condition cleared, edema less; no fall in blood pressure
	1500	May, 1946	13	Patient died 6/30/46; autopsy: subarachnoid hemorrhage, Crooke's changes, chromophobe adenoma, adrenals 15 gm., normal
R. W. M, 33	1300	Dec., 1946	18	Improved; bilateral biopsy of adrenals 1946—no tumor found; in 4 months weight down 20 lb.; blood pressure down from 146/112 to 124/76; also received methyl testosterone 80 mg. per day Jan.–Apr. 1947; remission until Apr. 1949; coronary occlusion 1949, thrombophlebitis 1950
	2800	Nov., 1950	31	No improvement; given 1750 Rɸ (tumor dose) to adrenals May 1951 in 15 days without immediate improvement
B. C. F, 31	950	Nov., 1946	14	No improvement
	950	Dec., 1946	12	
	Radon seeds§	June, 1947	.....	Improved; some paling of acne rosacea and striae, return of menses
C. T. M, 17	2300	Nov., 1948	23	Improved; biopsy of right adrenal 1948; no tumor found; within 6 mo. weight down, 11-oxysteroid excretion down to normal; continued improvement to present
C. C. F, 29	3350	Apr., 1951	26	Improved; within 4 mo. weight down 6 lb., resumption of menses, some clearing of paranoid tendencies, decrease in facial swelling; recurrence in 6 mo.

TABLE V.—(*Continued*)

Pt., Sex, Age	Tumor dose (Rf)	Date Therapy Started	Duration of Therapy (days)	Results
D. W. F, 40	2500	Dec., 1947	28	Complete remission; methyl testosterone 60 mg. daily Apr.–June 1948; 580 Rf (tumor dose) to each adrenal July 1948 given in 27 days; menses recurred Oct. 1948, 12 lb. weight loss by Dec. 1948; by Oct. 1949 in complete remission; weight down 34 lb., blood pressure normal, glucose tolerance curve normal; uneventful pregnancy terminated in normal delivery 1951
C. R. F. F, 24	1500 } Total 1100 } 6000 Rf 1900 } in 6 mo. 1500 }	Nov., 1932 Jan., 1933 Feb., 1933 May, 1933	11 12 20 18	Remission; within a year, return of menses; 40 lb. weight loss, less hirsute, glucose tolerance curve less abnormal, spine recalcified; abnormal mental reactions persist, otherwise remission continues to present (1950)
M. F. F, 17	800	Mar., 1931	28	Complete remission; menses became regular; weight fell 43 lb., striae faded, glucose tolerance curve became more normal; bones recalcified; remission continues to present (1950)

* Given in Peru; duration of therapy not known, dosage approximate; autopsy at New Haven Hospital.
† Given at Grasslands Hospital = dose in air.
‡ Autopsy at Barnert Memorial Hospital, Paterson, N. J.
§ Implanted by Dr. Leo Davidoff of Montefiore Hospital, New York, N. Y.

documented myocardial infarctions. Three patients (R. R., R. W. and L. P.) have had pulmonary infarctions.

Therapeutic Regimen (*Tables* IV *and* V). Nonspecific measures such as thyroid and diet have not been considered. Nineteen of the thirty-three patients in the present series received pituitary irradiation. The dosage schedules employed, tumor dose and results are presented in Table V. In three patients complete remission of the syndrome occurred. In two of these (C. R. F. and M. F.) radiation to the pituitary was the only therapy employed and the follow-up period in both patients has been a long one. In the case of D. W. it is difficult to judge whether pituitary irradiation, methyl testosterone or adrenal irradiation should be credited with her dramatic improvement. Six other patients showed some degree of improvement. Three of these, B. C. (who received radon seeds), C. T. and S. K. have maintained their improvement to the present, although the follow-up of only six months in S. K. is too short to permit any final conclusions to be drawn. The three other patients (M. deG., C. C. and R. W.) showed a favorable response but the improvement was temporary. In Case R. W. the improvement also coincided with methyl testosterone administration. Case M. deG. died so shortly after her second course of pituitary irradiation that its effect cannot be determined. Case R. W. did not respond to a second course of pituitary x-ray or, so far, to adrenal irradiation. Ten patients showed no response to pituitary irradiation. In cases R. A. and H. P. this might well be due to the fact that in these two patients a benign adrenal cortical adenoma was present. Of the remaining eight patients, one (M. deT.) remains under observation, one has enjoyed a spontaneous remission of her disease (R. C.), and the remaining six are dead. Cases G. O. and M. deG., both of whom died within three weeks of completing x-ray treatment, showed Crooke's changes in the pituitary.

Since the number of patients showing improvement is small and the amount of irradiation and the time over which this was given varied greatly, no conclusions can be drawn as to the optimal schedule to employ.

Adrenal irradiation has been employed in three patients. (Table IV.) In Case J. T. and, to date, in Case R. W., it has been without effect. In Case D. W. although the dosage directed at the adrenal area was small, it may have contributed to her improvement.

Prolonged use of androgens has been tried in only two patients, D. W. and R. W. Although both these patients improved it is difficult to evaluate the androgen effect because of previous and subsequent irradiation. Case J. T. received

a short course of methyl testosterone, with aggravation of her emotional instability. Cases A. K., H. P. and M. N. also received methyl testosterone briefly preoperatively without obvious effect. Hence, the experience in the present series cannot be compared with that of Albright.[133]

TABLE VI
RESULTS OF ADRENAL OPERATION IN CUSHING'S SYNDROME (SEVENTEEN PATIENTS)

Operation	No. Cases	Cured	Improved	Unimproved	Died
Removal of a benign tumor	5	2	0	0	3
Partial removal of carcinoma	1	..	1*	..	..
Biopsy of one or both glands, with or without partial resection	9	..	..	9†	..
Exploration	2	..	..	1	1

* Improvement temporary.
† Patient H. Hur. subsequently had bilateral subtotal adrenalectomy at Mayo Clinic with improvement.

None of the patients in this series received prolonged therapy with estrogens as reported by Rakoff and Cantarow.[143]

In seventeen patients in this series the adrenal areas were explored. (Table VI). A unilateral benign tumor was found in five and removed; of these two subsequently enjoyed complete remission of their disease while three died postoperatively. An adrenal carcinoma was found in one patient who improved temporarily after its removal but later died of metastases. Cortical hyperplasia was found in eleven instances, in nine of which biopsies were obtained. In one case (S. K.) four-fifths of one adrenal was removed; in another (R. C.) a partial resection was done bilaterally. The clinical course subsequently was unchanged in the nine patients biopsied and in one of the two explored. The other patient, (A. G.), developed a hemolytic streptococcal wound infection following exploration and died. In one patient, (H. Hur.), bilateral hemiadrenalectomy was subsequently performed at the Mayo Clinic with considerable improvement.

Postmortem Findings (*Table* VII). A review of the seven autopsied cases from the Columbia series, together with 107 postmortem examinations reported in the literature, indicates that bacterial infection is the leading cause of death in these patients (46.6 per cent). This is true both of those patients dying before and after the advent of antibiotic agents. About 27 per cent died in cardiac failure and another 13 per cent died of cardiovascular accidents or renal insufficiency, making cardiovascular complications a cause of death in 40 per cent of these young, predominantly female, adults. Major operations on these patients carry real hazards, twenty-three dying postoperatively. In a number of these death was ascribed to adrenal insufficiency following the removal of a functioning tumor. In others death was ascribable to severe wound infection. Although seventeen had primary carcinomatous changes in the adrenals, in only six was the adrenal neoplasm listed as the primary cause of death. Of particular interest are the six cases of the syndrome associated with tumors of the thymus[33,61,69,81,118] and four associated with carcinoma in the pancreas.[27,69,84,88] McLetchie considered the tumor in his patient to represent an adrenal rest; however, the fact that there was hyperplasia rather than atrophy of the remaining tissue (as would be expected with a functioning adrenal tumor) has led us to include this patient among pancreatic neoplasms. One patient[68] died of metastases from a sympathicoblastoma. Adding all patients in which neoplasms other than those involving adrenal or pituitary glands were present, the figure of 10 per cent is reached. In view of this, it is surprising that in the Columbia series only pituitary or adrenal neoplasms were encountered.

TABLE VII
CAUSES OF DEATH IN CUSHING'S SYNDROME (114 CASES)
(Multiple Causes Listed in Thirty-six Instances)

Infection	54	(6 tuberculosis, in 3 others tuberculosis present)
Cardiac failure	30	
Cerebrovascular accidents	8	
Uremia	6	
Postoperative deaths	23	(8 in adrenal insufficiency)
Carcinoma of adrenal	6	(in 11 others, carcinoma present)
Tumor of thymus	6	
Carcinoma of pancreas	4	
Sympathicoblastoma	1	
Acute gastrointestinal hemorrhage	2	
Pulmonary infarction	4	
Renal colic	1	
Asthenia	2	
Suicide	2	
Not listed	4	

In Table VIII the findings in the pituitary and adrenal glands for the ninety-seven cases in which adequate histologic data are available on both these glands are charted to show their interrelationship. In all but four instances in which search was made, Crooke's changes were

observed, the exception being the cases of Jacobi and Tigges,[64] Urban,[125] Pons et al.[105] and Metzger et al.[89] The last author reported that no such changes were visible in the basophilic adenoma of his patient but did not mention specifically the absence of the hyalinization in the remainder of the pituitary basophils where the Crooke's changes are most characteristically found.

The pituitary findings (Table VIII) are consistent with previous reports.[144] Adenomas of the gland were found in forty-seven patients and in thirty-one of these the tumor was of basophilic character. In seven the tumor was chromophobic and in one of these it was carcinomatous with metastases in the liver;[41] in three it was composed of a mixture of chromophobe and basophilic elements; in two eosinophilic adenomas were present while in one a mixed chromophobe-eosinophilic tumor was noted. In six patients the pituitary was reported as normal. In one of these[54] the presence of Crooke's changes was specifically denied.

TABLE VIII

RELATION BETWEEN PITUITARY AND ADRENAL LESIONS
(NINETY-SEVEN AUTOPSIED CASES—CUSHING'S SYNDROME)

Pituitary Findings	Adrenal Findings						Total
	Hyperplasia of Adrenals	Carcinoma of Adrenals	Unilateral* Benign Tumor with Atrophy of Opposite Gland	Hemorrhage or Infarcts in One or Both Adrenals	Hypoplasia of Adrenals	Normal Adrenals	
Crooke's hyalinization without other pituitary abnormality	17†	10††	5	..	..		33
Basophilic adenoma	24‡	..	1‡‡	2	1	3§§	31
Increased number basophils or basophilic invasion of posterior lobe	4§	1	1	..	..	2§	8
Mixed basophilic-chromophobe adenoma	3	..	..	..	..	..	3
Chromophobe adenoma	5**	1	..	..	..	1	7
Mixed chromophobe-eosinophilic adenoma	1	..	..	..	..	..	1
Eosinophilic adenoma	1	1	..	..	..	..	2
Increased number eosinophiles	..	1	..	..	..	..	1
Unspecified adenoma	1	..	1	..	..	1	3
Atrophy and fibrosis	1	..	..	..	..	..	1
Scar destroying neurohypophysis and pars intermedia	..	..	..	..	..	1	1
Normal	1	2	3	..	..	..	6
Total	58	16	11	2	1	9	97

* Includes two cases with unilateral hypertrophy of one adrenal without actual tumor.

† Five of these with thymic tumors; 2 with carcinoma of pancreas; 1 with sympathicoblastoma; 2 with changes in paraventricular nuclei.

‡ One of these with no Crooke's changes; 1 with a thymic tumor; 2 with changes in paraventricular nuclei.

§ One of these with no Crooke's changes.

** One of these chromophobe tumor was a carcinoma; 1 of these with carcinoma of pancreas, an intermediate cell pituitary tumor in addition to two chromophobe tumors; 1 with changes in paraventricular nuclei.

†† Two with changes in paraventricular nuclei.

‡‡ Changes in paraventricular nuclei.

§§ One with no Crooke's changes in the adenoma, 1 with ovarian tumor, ? adrenal rest.

The most common finding in the adrenals in fifty-eight cases was bilateral enlargement, frequently with multiple small adenomas. In sixteen carcinomatous changes were present.* In only nine was the abnormality most amenable to therapy, i.e., a unilateral benign adenoma, present. In two cases[129—case 2; 8—case 3] one adrenal gland was described as hypertrophied, the

* In the seventeenth case of adrenal carcinoma, the pituitary was not examined, hence this case is not included in Table VIII.

other being normal or atrophied. In seven instances the glands were reported as normal. While certain of these reports of "normal adrenals" leave no question in the mind of the reader, in others documentation of the normal character of the glands, with organ weights and histologic studies, is fragmentary. Hence, if anything, the number of patients stated to have normal adrenals errs on the high side. One case[42] is reported as having bilateral hypoplasia histologically although the measurements given of adrenal size (5 by 4 by 8 cm. for the right, and the left reported to be similar) would indicate the glands were relatively large.

Table VIII indicates the extraordinarily variable combination of pituitary and adrenal abnormalities which may be found in Cushing's syndrome. In all, twenty-eight different combinations have been described, the five most common in order of their frequency being (1) basophilic adenoma with adrenal hyperplasia, (2) no pituitary lesion other than Crooke's changes with adrenal hyperplasia, (3) no pituitary lesion other than Crooke's changes with either an adrenal carcinoma or (4) a unilateral benign tumor of adrenal or unilateral hypertrophy and (5) chromophobe adenoma of the pituitary with adrenal hyperplasia.

Osteoporosis was reported in seventy of the eighty-three patients for whom the degree of calcification was mentioned. Arteriosclerosis varying from minimal lesions in the aorta to extensive generalized arteriosclerosis was noted in fifty of the fifty-six patients examined for this abnormality. Pulmonary or myocardial infarctions were found to be present in sixteen of twenty-six patients in whom the possibility of this complication was mentioned.

COMMENTS

Thirty-two of thirty-three patients with Cushing's syndrome have been followed to date or to death. The average follow-up in the living patients is nine years from onset of symptoms while the patients who died did so after an average of four and a half years of disease.

The findings in the thirty-three patients with Cushing's syndrome who comprise the present series in general agree very satisfactorily with the previously established clinical picture of this syndrome. Two exceptions are apparent. In the present group mental disturbances occurred with significantly greater frequency than has been reported heretofore and likewise the susceptibility to infection and/or poor wound healing was more impressive. The reasons for these discrepancies are not immediately apparent. It is possible that the long follow-up which obtained in this group of patients permitted exhibition of these abnormalities whereas a number of the previous reports are based upon briefer periods of observation.

Obesity of the "buffalo" type and hypertension remain a hallmark of the syndrome. Hirsutism, while frequent, is seldom extensive or associated with definite masculinization.

Although amenorrhea is the rule, one patient (E. G.) in the present series became pregnant while apparently hyperadrenal. She had received no treatment other than one estrogen-induced menstrual period prior to the onset of pregnancy. She subsequently delivered a stillborn child at term. Dr. A. P. Forbes has written us of another patient with Cushing's syndrome who also became pregnant while decidedly hyperadrenal. Two other patients subsequently have undergone successful pregnancies, one (D. W.) following treatment with methyl testosterone, pituitary and adrenal irradiation and clinical improvement, and the second (H. P.) following the removal of a benign adenoma with cure. While impotence in males is common, occasional testicular examinations have revealed active spermatogenesis. However, some alteration in gonadal function is the rule.

Examination of the laboratory data reveals three consistently abnormal findings in patients with Cushing's syndrome: (1) a diabetic glucose tolerance test, (2) unusually few circulating eosinophiles, and (3) elevation of the so-called "corticoid" excretion in the urine. Each of these findings is a reflection of the circulation of increased amounts of 11-oxysteroids, and is in keeping with the hypothesis that the syndrome represents hyperadrenalism. In regard to the abnormal glucose tolerance curves, it is of interest that in spite of the many patients showing a decreased carbohydrate tolerance, the fasting blood sugar was on the average normal, and frank diabetes occurred in a minority. Among the reported cases only one instance[101] was encountered of the syndrome associated with diabetic acidosis.

Another consistent finding was the presence of osteoporosis. Experimentally ACTH has been shown to inhibit the stimulating effects of growth hormone on bone,[145] and healing of bone is delayed in cortisone-treated rabbits with ex-

perimental fractures.[146] Recently, DeMartini, Grokoest and Ragan[158] have reported pathologic fractures occurring in patients with rheumatoid arthritis receiving cortisone over long periods of time.

Apart from these commonly found abnormalities, an occasional patient showed evidence of severe polycythemia, altered serum electrolytes or gynecomastia with an increased urinary excretion of estrogens. In the present series these abnormalities were seen most strikingly in patients with cortical hyperplasia. No satisfactory explanation of these infrequent findings is apparent. It may well be that hyperactivity of the adrenal cortex includes the production of a qualitatively altered pattern of steroids as well as quantitatively increased amounts of the normal steroids. It may also be postulated that individuals vary in their response to or in the intermediary metabolism of these same steroids. The patient with rheumatoid arthritis reported by Sprague et al.,[147] who developed the classical features of hypochloremic alkalosis while taking cortisone, is in keeping with this latter postulate. This picture of elevated serum sodium, depressed serum potassium and chlorides was first noted in dogs given large doses of desoxycorticosterone acetate.[148]

It is of interest, in view of the recent emphasis on the depressing effects of ACTH and cortisone upon thyroid function, that there was no consistent trend observed toward hypo- or hyperthyroidism in this group of patients. A comparison was made in the tests of thyroid function in patients with benign adrenal tumor and in those with cortical hyperplasia but both groups were found to include a number of high and low basal metabolic rates and serum cholesterols. The five cases in which radioactive iodine uptake studies were carried out all fell in the cortical hyperplasia group, and uptakes varied widely from the levels usually associated with myxedema to levels in the hyperthyroid range. (Table II.)

Finally, some comment is in order about the 17-ketosteroid excretion. In the present series of Cushing's syndrome the excretion of these substances was significantly higher in those patients with cortical hyperplasia than in those with a benign cortical tumor. It is possible that this is no more than a chance finding. However, it is tempting to suggest that the lower values in the latter group are related to pituitary suppression secondary to increased circulating adrenal hormone produced by the tumor, with resulting decrease in adrenal functions apart from the tumor itself. This is in keeping with the recognized atrophy of all adrenal tissue apart from the tumor and, in turn, explains the postoperative hypoadrenalism encountered in this group. The higher 17-ketosteroid values in the cortical hyperplasia group could be related to a pituitary origin of the disease in these patients with continued pituitary stimulation in spite of the high levels of circulating adrenal hormone.

At autopsy, apart from endocrine abnormalities, osteoporosis and arteriosclerosis are present in an exceedingly high percentage of patients. Because of the high incidence of arteriosclerosis found in autopsy material, it is difficult to evaluate the significance of this latter finding. However, the frequent instances of severe and generalized arteriosclerosis remain impressive since Cushing's syndrome is a disease most commonly affecting young adult females. One patient, (R. K.), a twenty-eight year old female, developed myocardial infarction and at autopsy had advanced generalized arteriosclerosis. Another, (R. W.), a twenty-six year old female, was found at autopsy to have advanced coronary sclerosis and nephrosclerosis.

The review of 114 autopsied patients reaffirms the fact that the peculiar hyalinization of the pituitary basophile, first pointed out by Crooke[2] and subsequently in this country by Thompson and Eisenhardt,[144] is a highly characteristic finding. This basophilic hyalinization in Cushing's syndrome is seen in patients with or without basophilic adenomas, with benign or malignant tumors of the adrenal as well as in instances of adrenal hyperplasia, and also in patients with hypothalamic lesions. Crooke in his initial paper pointed out the relative specificity of this change. In a review of 350 glands from patients dying of other causes, minor degrees of hyalinization were found only nine times. His material included twenty-eight cases of Bright's disease, ninety-five instances of infection and twenty patients with diabetes mellitus. No hyaline changes were seen in thirteen patients with pituitary neoplasms but without symptoms of hyperadrenalism. Crooke reported absence of this change in one case of the adrenogenital syndrome. However, Mellgren[88] has more recently noted its presence in his series of eight cases of virilism.

Laqueur[149] has reported the finding of characteristic Crooke's change in six of eight pituitary glands obtained at autopsy from

patients treated with cortisone. This author has suggested that hyalinization of the basophils represents storage of ACTH secretion. This attractive hypothesis offers an explanation for the universality of the Crooke's change in hyperadrenal states—the high level of circulating adrenal hormone, be this due to hyperplastic adrenals, benign or malignant tumor, might serve to suppress the release of endogenous ACTH and hence possibly lead to its storage.

Although these characteristic basophilic cell changes are almost universally present in Cushing's syndrome, the question of the origin of the initiating lesion remains unresolved. The answer may well be that lesions in more than one area may serve as the initiator. Certainly one can no longer adhere to Cushing's original contention that the basophilic adenoma of the pituitary is the primary cause of the syndrome. In the group of autopsied cases here reviewed descriptions of 114 pituitaries were reported; no tumor could be demonstrated in over 50 per cent and in only 27 per cent was the tumor basophilic. In those instances of the syndrome in which an adrenal carcinoma exists it is most probable that the adrenal is the site of the initiating lesion. The possibility that Cushing's syndrome arises from hypothalamic lesions, with the pituitary and adrenal affected secondarily, has been raised by Heinbecker.[8] However, the recent report of Castor et al.[150] that thalamic and hypothalamic lesions can be produced during ACTH or cortisone therapy introduces the possibility that such hypothalamic lesions may be the result rather than the cause of hyperadrenalism.

The most common adrenal abnormality encountered in this group of 114 autopsied cases was bilateral cortical hyperplasia with or without discrete adenomas. It is not clear whether this hyperplasia was primary or secondary to pituitary stimulation. Carcinomatous changes were present in 15 per cent. In only 8 per cent was a unilateral benign cortical adenoma found.

The finding of neoplasms of pancreas or thymus in 9 per cent of patients dying with Cushing's syndrome is of extraordinary interest. Whether these neoplasms were in some fashion causal agents of the syndrome or whether the presence of hyperadrenalism predisposed these patients to the development of such neoplasms remains wholly unknown. Only in Hubble's[61] case was an attempt made to remove the thymic tumor; and as this patient died immediately postoperatively, it is impossible to tell whether excision of the tumor would have affected the hyperadrenal state.

In the patients studied at Columbia-Presbyterian Medical Center complete disappearance of all features of the syndrome has followed successful removal of a benign cortical adenoma. The two patients who survived the stormy postoperative period have shown a dramatic return to normal. Apart from this small group with a unilateral benign adenoma, irradiation of the pituitary has afforded complete or partial improvement in nine of the nineteen patients so treated. (In two of these, methyl testosterone may have been a contributing factor in the improvement.) This result is similar to that reported by Sosman.[151]

It has been the purpose of the present authors to confine this review to unequivocal instances of the syndrome. However, a discussion of Cushing's syndrome would not be complete without some comment on the group of cases possessing certain features of Cushing's syndrome accompanied by tumors in the ovary. In 1944 Kepler et al.,[152] in reviewing this subject, presented thirteen cases collected from the literature and reported a fourteenth case. In Kepler's case and in the two cases reported by Rottino and McGrath[153] certain of the features of the syndrome were present but not all. In the remainder, masculinization of the patient dominated the clinical picture. Hypertension was mentioned in only one patient. Evidence of decreased carbohydrate tolerance was present in six of the fourteen. None showed osteoporosis. Autopsy was reported in only one of these patients.[154] This woman died in shock twenty hours after partial removal of a large ovarian tumor; the pituitary was normal and the adrenals described as small although the weights were not reported. Unfortunately the clinical data available on this patient include only the fact that she had an increased amount of facial hair and glycosuria. The nature of the ovarian tumor in these cases has occasioned considerable discussion. Corpus luteum and tissue from an adrenal rest have been considered possible sources. This group of patients with ovarian tumors has been omitted from the present series because in none was the clinical picture of Cushing's syndrome unequivocal.

When comparison is made between Cushing's syndrome and the forms of hyperadrenalism induced by ACTH or cortisone, the striking

similarity of the two conditions is immediately evident. The metamorphosis in facial appearance has been commented on frequently in patients on hormonal therapy, as have acne, hirsutism and even striae. Abnormal mental reactions and an increased susceptibility to infection have been noted. On the other hand, diabetic tolerance curves are less commonly seen in iatrogenic hyperadrenalism than in Cushing's syndrome, and temporary diabetes, though it certainly occurs,[155] is rare in patients receiving these hormones. Diabetic acidosis has yet to be reported following ACTH and cortisone. Likewise, hypertension is uncommon, so far, in the induced form of hyperadrenalism except in those patients with underlying renal disease.[156]

The similarity between Cushing's syndrome and the clinical state induced by ACTH or cortisone gives added weight to the generally held opinion that Cushing's syndrome represents hyperadrenalism.

From the viewpoint of the management of induced hyperadrenalism, this review of the spontaneous disease emphasizes possible hazards and suggests additional potential difficulties. It is well recognized that patients receiving ACTH or cortisone may develop abnormal mental reactions. It is, of course, impossible to assess exactly to what extent such abnormalities represent the reaction of the individual's own psychic pattern to the far-reaching changes in his underlying disease induced by these hormones and to what extent they relate to the hyperadrenal state *per se*. The high percentage of mental aberrations in the spontaneous disease would suggest that the latter factor is an important one.

Another possible hazard brought to light is that of infection. Infections accounted for almost half of the deaths in the group of 114 autopsied cases of Cushing's syndrome reviewed here. It is true that many of these cases antedated the advent of antibiotic therapy but it remains evident that hyperadrenal patients are more than usually susceptible to infection. In this group of 114 there were nine instances of tuberculosis, which is no greater than occurs in the general population, but in six it was the major cause of death. Recent experimental work has established the increased susceptibility of mice with induced hyperadrenalism to the tubercle bacillus.[157] In any event, it is apparent that patients receiving prolonged treatment with ACTH or cortisone must be followed closely for infections, and among these activation of tuberculosis must be considered.

Finally, two potential hazards should be mentioned—arteriosclerosis and osteoporosis. Both are the rule in Cushing's syndrome. In the induced hyperadrenal state evidence of arteriosclerosis or of osteoporosis has been demonstrated.[158,159] The close parallelism of the spontaneous and the induced forms of hyperadrenalism suggests that these two abnormalities may constitute a serious problem in the course of long-continued therapy.

CONCLUSIONS

1. The findings in thirty-three cases of Cushing's syndrome collected from the Columbia-Presbyterian Medical Center have been reported. Thirty-two of these patients have been followed either to date or until death. An additional 189 cases from the literature have been reviewed.

2. Seventeen of the thirty-three patients died within five years of the known onset of the disease. Fifteen are alive after an average of nine years of known disease.

3. The findings in the present group of patients with Cushing's syndrome were in general similar to those reported in the literature with the following exceptions: A higher incidence of (1) mental abnormalities and of (2) poor wound healing or unusual infection was observed.

4. The major forms of therapy considered were adrenal operation, pituitary irradiation and administration of sex hormones. The most dramatic improvement was seen following removal of a unilateral benign adenoma (two patients). In one patient with adrenal hyperplasia a striking spontaneous remission was observed.

5. A review of 114 autopsied cases—seven from the present series and 107 from the literature—revealed that the major causes of death were infection, complications of cardiovascular disease and neoplastic disease. An extremely high incidence of arteriosclerosis and osteoporosis was noted.

6. The close parallelism of the spontaneous and the induced forms of hyperadrenalism suggests potential hazards of long-term therapy with ACTH or cortisone.

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Seminars on Gastrointestinal Physiology

The Problem of Peptic Ulcer*

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PEPTIC ulcer is the product of a pathologic process as a result of which the gastroduodenal mucosa fails to withstand the digestive action of acid gastric juice. Hypersecretion characterizes duodenal ulcer; decreased tissue resistance predominates in gastric ulcer. Acid is indispensable to both processes but apparently it is not the only factor. The purpose of this paper is to review briefly the evidence concerned with these phases of peptic ulcer and to discuss related clinical aspects.

ROLE OF ACID GASTRIC JUICE

Experimental Observations. Acid gastric juice can digest all living tissue including the stomach;[1–5] the digestive power is in proportion to the quantity of acid and pepsin. Ordinarily, the gastroduodenal mucosa is not exposed to pure gastric juice. Secretion of acid by the normal stomach is intermittent; the juice, furthermore, is rapidly diluted, buffered and neutralized by swallowed food and saliva, by mucus, and by the regurgitation of intestinal, pancreatic and biliary secretions. Interference with these mechanisms, exposing the gastroduodenal or jejunal mucosa to sustained maximum concentrations of hydrochloric acid, produces subacute and chronic ulceration in animals.[6]

Hypersecretion of acid may be induced experimentally by constant sham feeding,[7] by the retention of acid secretion in gastric pouches,[8–10] the continuous instillation of hydrochloric acid into the stomach,[11,12] explanation of the gastric antrum into the colon,[13] the injection of caffein[14] and by the administration of histamine in beeswax.[15] Elimination of the alkaline pancreatic juice by total pancreatectomy or ligation of the pancreatic ducts increases the incidence of histamine-induced ulcers in dogs.[16] Conversely, removal of the acid secreting cells by total gastrectomy prevents ulceration of the esophagus, small intestine or colon after the injection of histamine.[17] The ulcers complicating extensive cutaneous burns[18,19] also may be attributed to acid digestion of a mucosa more susceptible to injury probably because of edema and congestion.[20] Histamine levels in the blood are increased.[21] The histamine content of the gastric juice under these conditions is not known. However, the concurrent administration of histamine significantly increases the incidence of ulceration in burned animals.[20] The final stage of ulceration is a corrosive rather than an infectious process.[22] Injury to the adrenal glands removes an important defense to stress and probably intensifies the process although the mechanism is not clear. Adrenal cortical stimulation might predispose to the ulceration accompanying cutaneous burns but direct evidence of this relationship is not available.

Diversion of the alkaline intestinal content to the ileum by duodenoileostomy and the establishment of a gastrojejunostomy, the classic Mann-Williamson operation, invariably causes ulceration of the jejunum.[23,24] The lesion results from digestion of a normal but vulnerable mucosa by gastric content more acid than usual,[25] chiefly because of the absence of the alkaline pancreatic and biliary fluids. Ulceration in Mann-Williamson dogs may be prevented partially or completely by surgical or medical measures decreasing or eliminating the secretion of acid.[26] The duodenal ulcers in dogs with external pancreatic fistulas and exclusion of the pancreatic secretion also seem attributable primarily to the unneutralized acid gastric contents.[27] The experimental ulcers resemble human peptic ulcer in their location, morphology, and in their tendency to penetrate, perforate and bleed. Since a chronic peptic ulcer rarely develops spontaneously in animals,

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its occurrence under these planned, albeit drastic, conditions can be ascribed directly to the digestive power of acid gastric juice. The experimental ulcers, like the clinical lesions, heal rapidly when completely protected from the acid gastric content; partial protection from acid results in slow and irregular healing with many complications.[28]

Similar ulcers have occurred in man after the administration of histamine[29,30] and when, in the treatment of pancreatic carcinoma, the bile duct is anastomosed to the jejunum distal to the gastroenterostomy stoma and the pancreatic duct is ligated.[31] The incidence of peptic ulcer increases also after obstruction to the flow of bile into the intestine; the mechanism probably consists of loss of the neutralizing and buffering properties of bile and bile salts, and exposure of the duodenum to higher concentrations of acid.[32–34]

Clinical Observations. Clinically, chronic peptic ulcer develops only in those areas of the digestive tract exposed to the action of acid gastric content, namely, the lower end of the esophagus, the stomach, first portion of the duodenum, the small bowel adjoining a patent gastroenterostomy, or in a Meckel's diverticulum containing acid-secreting gastric mucosa. It occurs only in individuals producing hydrochloric acid; in those with a low rate of secretion as well as those with hypersecretion.[35,36] Free acid has been demonstrated in all of approximately 4,000 patients with duodenal ulcer and 750 patients with gastric ulcer observed by us during the past twenty-five years. Chronic peptic ulcer does not occur in patients with complete and persistent anacidity, namely, pernicious anemia and "spontaneous" achlorhydria.[37–41] Small ulcers, not demonstrable by x-ray but visible gastroscopically, may develop temporarily in a thin, atrophic gastric mucosa secreting little or no acid.[42] The ulcers are acute and they heal rapidly. Their occurrence emphasizes the fragility and vulnerability of the atrophic gastric mucosa; however, in the absence of hydrochloric acid the erosions do not progress to chronicity. The alleged instances of chronic peptic ulcer and anacidity reported in the literature are not convincing because of inadequate study of gastric secretion or insufficient evidence of an active chronic ulcer.[43] The test meals often employed to measure secretion do not accurately reflect the gastric secretory potential. Gastric analysis for this purpose requires the parenteral use of histamine, a histamine analog[44] or an equally potent secretory stimulant. Careful technic with positioning of the tube under fluoroscopic guidance to the level of the antrum also is important. Repeated tests may be necessary since occasionally in gastric ulcer the parietal cells temporarily fail to respond to histamine stimulation;[45,46] the histamine may be administered alone in a single dose, given together with 50 cc. of 7 per cent alcohol by mouth, or injected repeatedly at intervals, as in the continuous histamine test.

The development of anacidity in patients with peptic ulcer, either spontaneously or after gastric irradiation,[47] leads to complete healing; there is no recurrence for the duration of the anacidity. The frequency of jejunal ulcer after posterior gastroenterostomy in patients with duodenal ulcer is attributable to the gastric hypersecretion; the absence of jejunal ulcer after gastroenterostomy in patients with gastric ulcer or gastric cancer is readily explained on the basis of the low secretion or absence of acid.

Gastric Secretion. The mechanism of formation of hydrochloric acid remains incompletely understood although intensive investigation of the problem continues.[48–50] Certain clinical aspects of the problem have been studied in detail. The rate of gastric secretion in man is not constant; there are wide individual variations. Nevertheless, the volume of secretion, concentration of free hydrochloric acid and output of acid are significantly and unequivocally increased in the majority of patients with duodenal ulcer.[51–54] The hypersecretion is abnormal in that it persists continuously in the absence of the usual stimuli for secretion, that is, between meals and during the night. Absolute hyperacidity need not occur although the acid values are almost always higher than normal. In the twelve-hour nocturnal gastric secretion the average volume and free acidity exceed normal values twofold (Table I); the output of acid is three to four times greater than normal. The nocturnal hypersecretion persists after the healing of active duodenal ulcer.[55] (Table II.) It may be pertinent in this connection to indicate the need for additional measurements of gastric secretion before and after the healing of peptic ulcer; follow-up studies of those "normal" subjects with gastric hypersecretion also would be important. A potentially more fascinating although more difficult problem might be the long-term study of gastric secretion

in the same person to determine whether or not the tendency to hypersecretion is apparent early in life or is acquired later, perhaps as a consequence of chronic stress. The children of ulcer patients might be an appropriate group for this purpose since Meyer and his colleagues[56]

TABLE I
AVERAGE TWELVE-HOUR NOCTURNAL GASTRIC SECRETION

	Vol. (ml.)	Free HCl (c.u.)	Output HCl (mg.)
Normal	581	29	661
Duodenal ulcer	1,004	61	2,242
Gastric ulcer	600	21	454

TABLE II
AVERAGE TWELVE-HOUR NOCTURNAL GASTRIC SECRETION IN UNCOMPLICATED DUODENAL ULCER BEFORE AND AFTER HEALING

	Vol. (ml.)	Free HCl (c.u.)	Output HCl (mg.)
Active	1,047	58	2,208
Healed	1,002	54	1,957

observed a rather high "basal" acidity in single tests of gastric secretion among healthy relatives of ulcer patients. Excessive outputs of acid are demonstrable also in the twenty-four-hour fasting[57] and one-hour fasting basal secretion.[58,59] (Tables III and IV.) The gastric hyperreactivity in duodenal ulcer is evident also in the excessive and prolonged response to test meals, insulin-hypoglycemia,[60] histamine,[61] alcohol and caffein.[62,63] The volume and concentration of acid in histamine-stimulated secretion are high; however, because of the elevated basal secretion, the gradients of increase appear less than in the normal stomach.

"Hyper-hypersecretion" of acid is demonstrable in a smaller number of patients with refractory or intractable duodenal ulcer.[64] The outputs of acid in these cases often exceed 5,000 mg. per twelve hours, more than double the average for ordinary duodenal ulcer. The tremendous secretion is extremely difficult to neutralize or inhibit; the clinical course is characterized by severe ulcer pain and frequently is complicated by hemorrhage and perforation. Gastric resection and vagotomy also may not diminish the excessive output of acid. In Machella's case[65] the hyper-hypersecretion persisted after two vagotomies and a partial gastric resection; the postoperative course was complicated by three jejunal ulcers and by hypoproteinemia. Total gastrectomy was necessary to achieve complete and permanent anacidity and to effect a cure. In one of our patients[64] the enormous output of hydrochloric acid persisted despite extensive gastric resection including the antrum and transthoracic and transabdominal vagotomies; the patient died of persistent massive hemorrhage arising in a large jejunal ulcer.

TABLE III
AVERAGE TWENTY-FOUR-HOUR CONTINUOUS FASTING GASTRIC SECRETION

	Vol. (ml.)	Free HCl (c.u.)	Output HCl (mg.)
Normal	1,072	49	1,900
Duodenal ulcer	1,950	57	4,020
Gastric ulcer	1,048	22	922

TABLE IV
AVERAGE ONE-HOUR BASAL AND HISTAMINE-STIMULATED GASTRIC SECRETION

	Basal			Histamine		
	Vol. (ml.)	Free HCl (c.u.)	Output HCl (mg.)	Vol. (ml.)	Free HCl (c.u.)	Output HCl (mg.)
Normal						
Male	79	26	94	133	70	373
Female	65	21	59	101	56	225
Duodenal ulcer						
Male	110	51	215	201	92	684
Female	89	29	105	132	71	352
Gastric ulcer						
Male	81	28	84	111	54	221
Female	77	4	12	84	32	97

The pH of the intestinal content in the region of the duodenal bulb is more acid than normal.[66–68] The higher duodenal acidity presumably is attributable to the excessive gastric secretion and rapid gastric emptying. Berk et al. did not find a constant relationship between the simultaneously measured acidity in the stomach and the reaction of the duodenal contents. The evidence indicated that gastric acidity *per se* is but one of the mechanisms regulating the reaction of the duodenal contents; the possibility of deficient duodenal neutralization as an additional factor in the pathogenesis of chronic duodenal ulcer was suggested. No evidence of a decrease in the pancreatic[69] and

biliary secretions in duodenal ulcer has been demonstrated thus far. The secretion from Brunner's glands in the duodenum appears not to have been studied in peptic ulcer. Theoretically, atrophy of these glands and diminution or absence of their secretion might contribute to the more acid reaction of the duodenal contents in duodenal ulcer.

Pepsin, like acid, is secreted continuously, under the influence of the vagus nerves. The output of pepsin is greatly increased in duodenal ulcer.[70,71] Hydrochloric acid alone in sufficient concentrations is capable of injuring tissue cells; the presence of pepsin enormously increases the digestive power of acid.[72] Of the two factors, acid is the more important because, in gastric juice, acid is the regulator of peptic power.[73] Efforts to attach exclusive significance to one or the other would seem to be of little practical importance.

MECHANISM OF THE HYPERSECRETION

Parietal Cells. Numerous causes have been suggested for the gastric hypersecretion in duodenal ulcer. Histologic studies indicate a general correlation between the number of normal-appearing parietal cells in the mucosa of the fundus of the stomach and the production of hydrochloric acid; an inverse correlation seems to exist between the degree of atrophy and the number of parietal cells.[74–76] Parietal cells are relatively abundant in duodenal ulcer. Their number decreases progressively in benign gastric ulcer and gastric cancer without acid, to complete absence in pernicious anemia. Parietal cells apparently are demonstrable histologically in the stomachs of patients with complete anacidity.[77] Nevertheless, the hypersecretion in duodenal ulcer seems related anatomically, at least, to a larger parietal cell mass; the cells also may be functioning at a higher rate than normal. The increased number of parietal cells in the stomachs of guinea pigs after prolonged stimulation with histamine[78] suggests a "work hyperplasia." Thus the larger parietal cell mass in duodenal ulcer may result from chronic stress, mediated by vagal and/or hormonal influences, continuously stimulating the gastric glands.

Histamine. The release of histamine or a related substance from the ulcer or as a consequence of vagal and hormonal stimulation also has been suggested as a cause of the hypersecretion. There is no satisfactory evidence of a significant increase in the histamine content of the blood in duodenal ulcer.[78,80] Indeed, there is no conclusive proof that the histamine content of the blood is directly correlated with the rate of gastric secretion. Gregory[81] could not find significant differences in the histamine activity of plasma samples from the portal and systemic venous blood taken from unanesthetized dogs before and after a meat meal. There is some indication that the histamine content of gastric juice is directly correlated with the rate of gastric secretion[82] although the data are difficult to evaluate conclusively. Perhaps of more importance is the similarity in the histamine activity extractable from the gastric mucosa between acid-secreting stomachs (peptic ulcer) and achlorhydric stomachs (carcinoma).[83] If histamine liberated from the ulcer area caused the excessive output of acid, the hypersecretion should subside with healing of the ulcer; since the high outputs continue after healing, such a mechanism appears unlikely.

Enterogastrone is the hormone released from the mucosa of the small intestine in the presence of fat or fatty acids and responsible physiologically for the inhibition of gastric secretion and motility accompanying the ingestion of fat.[84,85] The hypersecretion in duodenal ulcer theoretically might be attributed to a failure or interference with this physiologic mechanism in the duodenum;[86,87] however, conclusive evidence for this postulated abnormality has not been presented thus far. Again, the persistent hypersecretion after the healing of duodenal ulcer would not appear to support this view.

Hyperactivity of Gastric Antrum. Recent studies by Dragstedt and his co-workers[88] and by others[89] have confirmed Edkins'[90] view that gastric secretion is stimulated, in part, by a hormone, gastrin, produced by the mucosa of the antrum of the stomach. Complete removal of the antrum in dogs profoundly decreases the output of hydrochloric acid. Transplantation of the antrum into the duodenum or colon in dogs with totally isolated gastric pouches results in sustained hypersecretion of acid and the development of gastrojejunal ulceration. The hypersecretion occurs in the absence of all vagal connections, indicating that the antrum functions as a specific endocrine organ. Nevertheless, experimental evidence suggests a relationship between the antral and vagal mechanisms, as noted later in this paper. These observations clearly indicate that hyperactivity of the antral

mechanism plays a significant role in the gastric secretion of the dog. A similarly vital function has not yet been established in man. Removal of the antrum during partial gastrectomy is alleged to contribute to the post-gastrectomy reduction in gastric secretion; however, the hypersecretion of duodenal ulcer may persist despite resection of the antrum.

Adrenal Steroids. The prolonged administration of large quantities of corticotropin or cortisone increases the volume of secretion and the concentrations of acid and pepsin in the basal and nocturnal gastric secretion.[91,92] The increase may be from normal values to levels characteristic of duodenal ulcer.[91] The secretory response resembles that to be expected from vagal stimulation but it has been demonstrated also in patients previously having undergone successful vagotomy.[93] In dogs ACTH stimulated the output of hydrochloric acid in the presence and absence of both the vagal or antral mechanisms.[94] Parenterally administered saline apparently produced a greater increase in the volume of gastric secretion in pylorus-ligated rats than that induced by cortisone, adrenal cortical extract or desoxycorticosterone.[95] Urinary uropepsin, a proteolytic enzyme originating in the pepsinogen secreted by the stomach into the blood and varying directly with pepsin secretion by the stomach,[96–99] also increases during the administration of corticotropin or cortisone.[100,101] This effect is not observed in patients after total removal of the stomach, in the gastric atrophy accompanying pernicious anemia, and in patients with adrenal insufficiency. The hypersecretion not infrequently precipitates the recurrence of peptic ulcer and the complications of hemorrhage or perforation.[91,92,102–108] The ulcers histologically are acute, necrosing lesions; there is no evidence of vascular disease or thrombosis. These observations have led to the thesis that emotional or systemic stress induces the hypothalamus to produce a humoral agent stimulating the pituitary secretion of corticotropin.[91] The corticotropin acts upon the adrenal cortex, releasing steroid hormones, cortisone and cortisone-like substances, stimulating the gastric glands to secrete acid and pepsin; the mode of action of the steroids is not yet clear. This concept provides an interesting and plausible explanation for the ulcers occurring experimentally during infection, burns, shock, anoxemia and muscular fatigue;[109] it also may indicate an important mechanism for the ulcers developing in man after sustained emotional conflict. The hypersecretion of duodenal ulcer thus might be attributable to increased activity of the hypothalamus-pituitary-adrenal axis and to excessive stimulation of the gastric glands by adrenal steroids. However, the nature of the abnormal hypothalamic activity is unexplained and the possibility that it may be produced by other factors, not psychogenic in origin, is not excluded. Direct evidence of adrenal cortical hyperactivity in the absence of steroid therapy has not been obtained thus far in duodenal ulcer. Furthermore, this concept would not seem equally applicable to gastric ulcer, in view of the normal or subnormal outputs of acid. *A priori*, a high incidence of peptic ulcer might be anticipated, on the basis of this theory, in patients with diseases accompanied by adrenal cortical hyperfunction; we have not encountered evidence of this to date.

Vagal Hyperactivity. Gastric secretion in man is predominantly nervous in origin.[110,111] The vagus nerves are the only known efferent neural pathways for such stimuli. Stimulation of the vagi or unopposed vagal activity (after sympathectomy)[112] elicits a copious secretion, rich in acid and pepsin. Hyperactivity of the sympathetic nerves decreases gastric secretion.[113,114] The nervous phase of secretion is not exclusively neurogenic in origin but probably is mediated also by a humoral mechanism,[115] perhaps involving gastrin or another histamine-like substance. It has been demonstrated, for example, that the gastric secretory response to vagal stimulation is decreased by cocainization or excision of the antral mucosa.[116] Complete division of the vagus nerves eliminates the nervous phase of secretion in patients with duodenal ulcer, greatly reducing the volume of gastric content and the concentration of free acid.[117] Vagotomy does not significantly depress the normal gastric secretion in man nor does it protect against the development of jejunal ulcers in dogs subjected to the Mann-Williamson operation.[118] These observations indicate that complete vagotomy depresses only the excessive outputs of acid, that the hypersecretion in duodenal ulcer is mediated by the vagal mechanism and, further, that vagal activity is increased. The basis for the presumed vagal hyperactivity is not known and the foregoing statement may be an oversimplification of the problem, especially since the neurogenic and hormonal

mechanisms of gastric secretion apparently function in an interdependent relationship. Since vagotomy decreases the gastric secretory response to secretory stimuli acting peripherally (histamine and caffein[119,120]) the hypersecretion may be attributable, in part at least, to parietal cell hyper-reactivity; the hyperactivity may be caused by the overproduction of acetylcholine, potentiating the response of the parietal cells to secretory stimuli. The secretory hyperactivity theoretically might be caused by hormonal stimulation, perhaps by adrenal steroids; or the vagal centers, for some unknown reason, may be functioning at an intrinsically higher level. A most interesting and, as yet, unanswered question is the possible direct or indirect relationship between vagal hyperactivity and underlying emotional disorders.

Emotional Disturbances. The stimulating effect of certain emotional states in man has been demonstrated frequently.[121–125] The observations include a rise in gastric acidity during periods of conscious anxiety and the development of hypersecretion, hypermotility, vascular engorgement and friability of the gastric mucosa in the subject Tom during periods of sustained resentment, hostility or anxiety. An increase in gastric acidity also has been elicited by the suggestion of palatable food to conscious subjects[126] and during hypnosis by sham-feeding;[127,128] the suggestion of pain or danger or a state of complete freedom from emotional conflict decreased the volume of secretion and produced anacidity.[129–131] Mirsky and his co-workers[132] also have demonstrated a rise in blood pepsinogen and urinary uropepsin in patients with peptic ulcer, especially during periods of significant personal conflict. However, the frequent association of hyperacidity with increased uropepsin excretion was regarded as fortuitous and attributable to as yet unidentified factors increasing either acid production by the stomach and/or uropepsin excretion. Winkelstein and his colleagues[133] studied a young woman with a large gastric fistula, by means of frequent psychoanalytic interviews and measurements of gastric secretion, motility and vascularity, and noted an apparent dissociation of gastric functions, suggesting that the concept of emotional disturbances causing symptoms and disease through an increase or decrease of the synchronous functions of an organ might require modification by the phenomenon of "dissociation." These observations clearly indicate the significant influence of emotional states upon gastric function in man under certain experimental conditions. It is noteworthy perhaps that the experimentally induced phenomena subside rapidly when the stimulus-provoking situation is removed; the gastric hypersecretion of duodenal ulcer does not appear so easily influenced. The findings suggest that emotional conflict may seriously disturb gastric function, if sustained, but they do not prove the relationship. Mahl[134] demonstrated a significant increase in the secretion of hydrochloric acid during experimentally induced chronic fear in dogs and monkeys; the augmented output of acid was not correlated with a significant decrease in blood sugar. These observations would indicate that the physiologic relationship between psyche and stomach is not the exclusive property of Homo sapiens.

The chronologic association between the onset or recurrences of peptic ulcer and sustained emotional tension, and the increased incidence of ulcer and perforation during prolonged stress and anxiety, as in the air raids over Europe and Okinawa,[135–138] demonstrate an important circumstantial relationship between emotional conflict and peptic ulcer. However, additional objective evidence seems desirable to support the view that psychogenic disturbances regularly cause gastric hyperfunction and that the hyperfunction alone initiates the development of chronic peptic ulcer. It is of interest in this connection that direct stimulation of the vagus nerves experimentally[139–141] or the prolonged administration of parasympathomimetic drugs[142] may produce mucosal hemorrhages and superficial gastric ulcerations but not chronic peptic ulcer; perhaps the problem is one of methodology rather than concept.

Emotional disorders are frequently observed in patients with peptic ulcer but the psychodynamics are variously described. The clinician recognizes many patients as tense, driving, overly conscientious, hypersensitive individuals. Sullivan and McKell[143] stress the craving for affection and the intense desire for superiority. Mittelmann and Wolff emphasize the role of anxiety, insecurity, resentment and guilt, with overt assertive independence. Alexander[144] defines the emotional problem psychoanalytically as a fundamental conflict between receptive and giving tendencies with attempts to abolish the conflict by overcompensation in the direction of giving. These characterizations of the ulcer patient appear to delineate the same emotional

problem but in differing descriptive terms. Alexander limited this conflict in peptic ulcer to the nine cases under his observation, did not insist upon the specificity of the disorder, and recognized also the importance of organic factors in the pathogenesis of peptic ulcer. However, as Stine and Ivy[145] point out in their excellent review, the same basic conflict now has been described in more than 300 patients. Interpretations of the electroencephalogram,[146] the Rorshach test[147] and of human figure drawings also have been interpreted as demonstrating the presence of strong passive, dependent and receptive tendencies in the ulcer patient. Szasz[148] has suggested the concept of "regressive innervation" producing a localized and presumably specific parasympathetic hypertonus when the organism is unable to deal with a stressful situation through appropriate adaptive behavior. These observations are interesting and persuasive. However, the psychoanalytic concept has not received complete acceptance. The subjective character of the studies together with the natural tendency to describe and to emphasize those patients with the more obvious emotional difficulties necessitate further investigation of the problem. Many ulcer patients clinically do not conform to the pattern of the tense, driving and successful individual but present rather a passive, receptive appearance; emotional stress is not always associated, at least overtly, with the onset or recurrence of the disease. More evidence is needed, therefore, to establish the assumption that typical psychodynamic patterns are present in all patients with peptic ulcer, that they are of specific significance in the disease or, indeed, that they cause peptic ulcer. Particular emphasis might be directed to the long-term study of more ulcer patients, gastric as well as duodenal, to the use of controls, including healthy persons and patients with other diseases, and to the development of more objective technics, such as the measurement of blood pepsinogen and urinary uropepsin. Many interesting questions await solution. For example, the increased gastric secretion during experimentally induced anxiety subsides promptly when the tension is relieved; in duodenal ulcer the hypersecretion persists despite healing of the crater; does this signify continued emotional stimulation (vagal, hormonal)? Assuming that the excessive output of acid is emotional in origin, is there any evidence that successful psychotherapy significantly and permanently decreases the hypersecretion? This may, indeed, be possible but such evidence has not come to our attention. What is the mechanism of the excessive nocturnal secretion and what are the implications of the evening rise in acidity? Are psychogenic factors merely excitatory, effective only in persons with a "basic susceptibility" to the disease?

Despite the many unsolved problems in this field, present evidence indicates that emotional disturbances do exist in many if not all patients with peptic ulcer and that nervous stress does play an important role in provoking acute ulcers or the recurrence of chronic ulcers. Furthermore, psychotherapy in the form of group or individual interviews and other supportive measures seems to be a valuable adjunct in the treatment of the disease.[149] The usefulness of psychoanalysis in therapy remains to be determined although its applicability would appear limited. Stine and Ivy recently have initiated a careful study of this problem. In seven patients with improvement in personality through psychoanalysis the clinical course of the ulcer seemed improved but only two patients failed to experience a recurrence of ulcer.

In concluding this phase of the ulcer problem, the evidence presented thus far does not appear to justify a uniform psychodynamic pattern applicable to all patients with peptic ulcer; nor is there complete understanding of the role of emotional disturbances in the pathogenesis of the disease. The accumulated clinical observations of the gastroenterologist and the psychiatrist rather tend to demonstrate variations in biologic findings and personality organization among ulcer patients. Apter[150] suggests adoption of the psychiatric concept of reaction-pattern as a useful method of correlating these observations meaningfully. Peptic ulcer then is regarded as "an end-result of the organism's adaptive failure and represents the consequences of second order adjustment." Apter's working hypothesis for schizophrenic reactions[150] paraphrased for peptic ulcer is as follows: "Biological factors are etiologically determining for some patients; emotional factors are prepotent for others; and there is a delicate but not yet understandable interrelation of emotional and biological factors for all patients with peptic ulcer. In future research, the intricate interplay of emotional vectors, as studied by the psychoanalytic psychiatrist, has to be matched by the gastroenterologist with equal attention and

understanding of variations in biological data[133] in the same patient. In this way, the unique contributions of the psychoanalytic psychiatrist, the microscopic examination of the person and his adaptive pattern, can be preserved." Further study will be required to determine the usefulness of this approach in distinguishing more clearly several types of ulcer patients and in assessing the relative importance of biologic and emotional factors in the etiology of the disease.

Neurogenic Factors. The development of peptic ulcer after intracranial operations or severe head injury[151–154] seems to be a related problem. Cushing postulated a parasympathetic center in the diencephalon connected with the cranial autonomic nerves. Autonomic imbalance and excessive activity of this center presumably caused hypersecretion, hypermotility and hypertonicity of the stomach, vascular spasm and areas of ischemia or hemorrhagic necrosis; the devitalized mucosa then succumbed to the digestive effect of hyperacid gastric juice. This hypothesis, though its postulated dynamics are in accord with current views, actually has never been established objectively in its entirety. Eppinger and Hess,[155] Von Bergmann and others suggested[156,157] an autonomic imbalance in peptic ulcer, characterized by hyperactivity of the parasympathetic nervous system; this assumption was based upon symptoms or physical findings considered to reflect vagal activity and upon the response to drugs stimulating or inhibiting the parasympathetic nervous system. The "vagotonic" concept, though generally accepted in Europe, never has received widespread approval in this country. It might be desirable to reinvestigate the problem by analysis of various physiologic functions correlated with different activities of the parasympathetic and sympathetic divisions of the autonomic nervous system, as developed by Wenger.[158] However, even then, interpretation of the data would be limited by the difficulties inherent in a subjective analysis and by the accuracy with which the various physiologic functions truly reflect autonomic imbalance.

Mucosal hemorrhages and erosions may occur in the upper digestive tract after experimental stimulation or injury to the hypothalamus; the site of the hypothalamic injury involves the tuberal and to a lesser extent the supra-optic regions.[159–160] Similar changes also may develop after mid-brain and pontine lesions and after transections of the spinal cord, all probably involving descending pathways in the autonomic system. The large destructive intracranial injuries apparently are more likely to precipitate the gastroduodenal lesions, for hemorrhages and erosions do not occur when the hypothalamic lesions are placed carefully and when the animals receive excellent pre- and postoperative care.[161] Sheehan,[159] in a detailed analysis of the experimental evidence, concludes that stimulation of the hypothalamus, particularly in the more posterior part of the lateral hypothalamic area, inhibited peristalsis, decreased muscle tone in the stomach, increased the mucous content of the gastric juice, with a tendency to diminished rate of flow. These effects were accompanied by sympathetic manifestations, such as dilatation of the pupils, widening of the palpebral fissure and a rise in blood pressure. Similar changes may be noted in the gastrointestinal tract after stimulation of the splanchnic nerves. Sheehan accepts the evidence for a sympathetic center in the hypothalamus regulating gastrointestinal activity but points out that the presence of a parasympathetic center, although likely, is less well established. According to Sheehan, the gastrointestinal changes may be attributed to an overactive sympathetic center in the hypothalamus, probably caused by irritation from the adjacent injury. Furthermore, "there appears to be a close similarity between these erosions, the lesions produced by peripheral nerve section and by bilateral adrenalectomy and the acute digestive crises accompanying tumors of the brain or following intracranial operations. However, the relationship of such gastrointestinal changes to peptic ulceration in man remains obscure. The hemorrhages and multiple mucosal erosions are found frequently in the lower end of the esophagus and in the cardiac end of the stomach. When they occur in the body of the stomach, they are located more often on the greater than the lesser curvature; they may be found also in the colon. The multiplicity of the erosions, their acute onset and rapid course are not usually observed in human peptic ulcer." Focal gastric hemorrhages also may occur after brain lesions in animals previously having undergone bilateral vagotomy, indicating that vagal activity is not indispensable to this process.

Similar lesions can be produced by the repeated administration of pilocarpine,[142,157] adrenaline, acetylcholine,[162,163] mecholyl,[151] histamine,[164] pitressin[165] and urecholine.[166] The ulcers are multiple, often occur on the greater

curvature or fundus of the stomach and they begin as focal hemorrhages; chronic ulceration is rare. The lesions appear to consist primarily of a vascular disturbance (spasm or perhaps hyperemia and capillary stasis), presumably causing local tissue anoxemia, mucosal ischemia and areas of susceptibility to acid and pepsin. Dodds and his co-workers[167] found that the gastric hemorrhages and ulcerations occurring after the administration of posterior pituitary extract were confined to areas containing acid-secreting cells. Animals continuously secreting acid gastric juice were most susceptible. The development of ulcerations could be prevented by neutralization of the gastric content. These observations emphasize the important contributory role of acid in the pathogenesis of the lesion. They suggest that the central nervous system somehow may play a significant role by increasing both the output of acid and the vulnerability of the gastroduodenal mucosa to the acid attack; perhaps hormonal agents and adrenal cortical steroids are of particular importance in this connection.

ROLE OF DECREASED TISSUE RESISTANCE

Gastric Ulcer and Duodenal Ulcer. Gastric ulcer resembles duodenal ulcer in symptoms, course and in the response to therapy. The pain mechanism, consisting of acid stimulation of exposed nerve endings, is identical in the two lesions. The complications are similar except that jejunal ulcer is uncommon after gastroenterostomy for gastric ulcer. The complete and permanent absence of acid, occurring "spontaneously" after gastric irradiation or as the result of surgery, leads to complete healing of both lesions. However, in striking contrast to the continuous hypersecretion in duodenal ulcer, the output of acid in gastric ulcer is intermittent and less than normal.[168] The secretion is not correlated with the location of the ulcer in the stomach, the age of the patient or the duration of symptoms; it is not lowered significantly by vagotomy.

In the absence of hypersecretion other factors such as decreased tissue resistance appear to be responsible for the failure of the mucosa to withstand the acid attack. The absence of diffuse ulceration and the circumscribed nature of peptic ulcer suggest local tissue vulnerability. However, new gastric ulcers often develop after local excision of the original ulcer; duodenal ulcers not infrequently are multiple; and jejunal ulcer is a common complication after posterior gastroenterostomy for duodenal ulcer, suggesting a more general tissue susceptibility. Nevertheless, it is difficult to explain on the basis of the acid factor alone the absence of peptic ulcer in persons secreting large quantities of acid, the presence of duodenal ulcer in occasional patients with normal outputs of acid or the healing of duodenal ulcer despite persistent hypersecretion of acid. It seems pertinent, therefore, to examine the evidence concerning tissue defenses and the resistance of the gastroduodenal mucosa to the acid attack.

The remarkable resistance of the gastroduodenal mucosa to acid digestion has been related to at least three factors:[169] the mucous barrier, the regenerative capacity of the mucosal cells and an adequate blood supply to the stomach; other mechanisms may be involved but there is no knowledge of their identity or mode of action.

Mucous Barrier. According to Hollander,[170] the gastric mucous barrier essentially comprises (1) the layer of viscous mucus covering the wall of the gastric cavity and (2) the layer of tall columnar cells immediately below the sheet of mucus, together with the low columnar and cuboidal cells lining the gastric crypts. The normally greater resistance of the gastric mucosa to acid and pepsin, in comparison with the duodenum and jejunum, may be attributable to this continuous layer of mucus-secreting cells not found in the intestine. The greater resistance of the duodenum, in comparison to the jejunum, has been related to the presence of Brunner's glands. Gastric mucus is secreted continuously. It protects the stomach by forming a more or less continuous thick, adherent layer over the surface. Protection also is afforded by the presence of mucus in the surface epithelial cells, the ability of mucus to adsorb and resist pepsin digestion and by its capacity to neutralize and buffer acid.[171–177] Many observers[178–181] have suggested deficiency of gastric mucus as a cause of gastroduodenal ulceration. Theoretically, in gastric ulcer the secretion of mucus may be insufficient because of decreased production by the surface cells, diminished regeneration of cells and fewer mucus-secreting cells (perhaps because of dietary deficiency or local vascular disturbances) and excessive removal of mucus by mucolytic enzymes. Evaluation of this problem has been handicapped by the varying

technics for measuring mucous secretion in the intact stomach and by uncertainty as to the relationship between the mucus content of gastric juice and the status of the mucus-cell layer. Thus far, no conclusive evidence has been adduced that the concentration and total quantity of mucin in the gastric content are decreased in peptic ulcer.[182-184] Tulin and his associates[185] could not demonstrate a statistically significant decrease in the concentration and content of total dissolved mucin under fasting conditions or after an alcohol test meal in patients with peptic ulcer and normal subjects. Similar findings were reported also in patients with gastric ulcer after the injection of histamine.[186] Glass and Boyd[187] studied this problem in sixty patients with peptic ulcer and 106 control subjects with various gastric disorders; measurements were made of the total dissolved mucin and its fractions:[188] dissolved mucoprotein from the gastric glands and dissolved mucoproteose from the surface epithelium lining the stomach. No evidence was found to indicate a deficiency of gastric mucin or its fractions in the fasting secretion, after stimulation with alcohol or histamine, and after central vagal stimulation with insulin in patients with gastric or duodenal ulcer. The output of gastric mucoprotein was increased significantly in patients with duodenal ulcer as compared with controls and with gastric ulcer, both in the fasting and insulin-stimulated gastric secretion; this observation was interpreted as in accord with the general pattern of hyperactivity of the gastric glands in patients with duodenal ulcer. Thus far, no objective evidence has been presented to suggest a defect in the mucus cells themselves, of primary importance in the development of peptic ulcer.[189] The careful investigations of the second line of defense, the layer of mucous epithelium, now in progress in Hollander's laboratory, may clarify the subject.[190] Attempts at replacement therapy with gastric mucin[191,192] or chondroitin[193] have been unsuccessful. The use of mucigogues, hydrogen peroxide,[194] oil of peppermint[195] and a 3 per cent emulsion of eugenol, has yielded equivocal results. As Hollander points out, it is doubtful whether exogenous therapy can substitute for the normal endogenous secretion of mucus. Lysozyme,[196] a mucolytic enzyme, is capable of damaging gastric and colonic mucosa in animals;[197] however, there is no conclusive evidence that lysozyme plays a significant primary role in the pathogenesis of peptic ulcer.[198]

Role of Gastric Atrophy. The tendency for gastric ulcer to occur on or near the lesser curvature of the body and antrum of the stomach has been attributed to a thinning of the mucosa in this area, the mechanical trauma of food as it passes along the lesser curvature to the duodenum, increased nerve supply to the region and to a less abundant blood supply. The gastric ulcers occurring in the presence of foreign bodies (bezoars) or diaphragmatic hernia and after injury to the abdominal wall suggest that mechanical factors may contribute to the development of the lesion;[199] however, such instances are uncommon and local trauma does not appear to play an important role generally. Although Konjetzny[200] found no significant difference in the appearance of the gastric mucosa in duodenal and gastric ulcer, more recent histologic[75] and gastroscopic studies[201] indicate a high incidence of mucosal atrophy in gastric ulcer. The mucosa is thin, fragile and susceptible to injury; hemorrhages and acute erosions are not uncommon. Normally, the gastric mucosa promptly replaces epithelial cells which are shed as a result of exposure to gastric irritants; rapid replacement of cells undoubtedly is an important part of the defense mechanism.[202,203] Perhaps, in the presence of atrophy of the gastric mucosa the regenerative capacity of the cells is diminished, resulting in fewer mucus-secreting cells, decreased production of mucus, greater exposure to acid and, consequently, increased vulnerability of the mucosa to minimal quantities of acid and pepsin. The constant association of gastric atrophy and pernicious anemia and the consistent absence of chronic peptic ulcer in pernicious anemia indicate that atrophy alone is not sufficient cause and that the presence of acid gastric content is required.

Endocrine abnormalities, hepatic disease, trophic nerve disturbances or intrinsic cellular abnormalities have been suggested as causes of decreased tissue resistance in peptic ulcer but there is no satisfactory evidence for these views.

Vascular Disturbances. The resistance of the gastroduodenal mucosa to acid digestion, in addition to the factors already mentioned, depends upon an adequate supply of blood. The old concept of peptic ulcer resulting from vascular thrombosis or embolism[204-207] producing an infarctive lesion has been discarded.

Thrombosis of vessels in the base of an ulcer is a result, not the cause, of the lesion. Almost all the blood vessels to the stomach may be ligated without producing ulceration; indeed, the procedure was utilized temporarily as a surgical treatment for peptic ulcer.[208] The tendency of peptic ulcer to increase in size, bleed and perforate indicates a penetrating lesion beginning in the mucosa and extending into the wall of the stomach or duodenum, a course incompatible with an infarctive lesion.

Barclay and Bentley[209] have demonstrated that the gastric mucosa is richly supplied with freely anastomosing blood vessels, almost completely filling the glandular layer like a vascular sponge. Furthermore, there are no end arteries, as had been assumed earlier.[210] The submucosa contains an extensive plexus of large vessels and also arteriovenous anastomoses, apparently under the control of the autonomic nervous system. Large channels thus exist capable of transferring considerable quantities of blood to and from the gastric mucosa, and presumably capable of decreasing the supply of blood to localized areas in the stomach. However, the significance of these arteriovenous shunts in the development of peptic ulcer remains to be established.[211] There is no conclusive evidence to support the concept of a neurovascular disturbance diverting blood from the stomach to other abdominal organs.[212] Key[213] observed hypervascularity rather than ischemia in association with gastric ulcer. De Busscher[214] and Betz,[215] utilizing different technics, also found no evidence of a deficient blood supply to the area of ulceration.

Under experimental conditions, gastric ulceration may occur after fat embolization of the capillaries to the stomach[216] and after vasoconstriction induced by repeated injections of pitressin, epinephrine and other agents. Venous stasis alone does not cause ulceration but it enhances the ulcer-producing effect of histamine;[217] shock and anemia also increase the development of gastric ulcers in animals.[218] The lesions are acute and they heal rapidly. The relationship of the experimentally induced vascular disturbances to chronic peptic ulcer in man is not yet proven. Babkin[111] and other observers attempted to relate the lesion to the action of histamine upon capillaries, increasing their permeability and producing capillary stasis and areas of ischemia and necrosis, more vulnerable to the acid attack. Necheles[219] and his co-workers emphasized the vasoconstrictive action of acetylcholine, presumably liberated in large quantities by the vagal nerve endings. Acetylcholine apparently has been demonstrated in the blood of patients with active peptic ulcer;[220] however, the observation has not been confirmed and its significance is not established. Apparently, no studies have been made comparing the acetylcholine content of normal and ulcer-bearing stomachs.[221] It may be noted also that vagal stimulation produces vasodilation rather than vasoconstriction. The concept of a generalized circulatory insufficiency intensified in focal areas of the stomach also has been proposed.[222] The nature of the presumed circulatory insufficiency is not clear; it has been attributed to depletion of protein, alterations in the chemical composition of the blood and to the presence of vasoconstrictor agents. More objective evidence is needed to evaluate these theories. In concluding this phase of the problem it seems reasonable to assume that vascular disturbances, such as vasoconstriction or hyperemia and capillary stasis, may contribute to the pathogenesis of peptic ulcer by creating mucosal areas more susceptible to the acid attack. Thus far, confirmatory objective evidence does not seem to have been adduced in man. Perhaps the solution of this problem awaits the development of technics for visualizing the gastric circulation *in vivo*, analogous to the studies of Barclay,[223] with micro-arteriography of resected stomachs. However, even if a vascular disturbance were to be demonstrated in peptic ulcer, this would not necessarily constitute the primary mechanism in the formation of ulcer; further study would be required to determine the cause of the vascular abnormality. It may be noted also that in practically all experimental situations emphasizing the vascular factor, the ulcerations were acute and multiple; a single chronic ulcer was not produced. Thus despite intensive investigation there continues to be no clear concept of what constitutes tissue resistance and tissue breakdown in peptic ulcer. Additional study of this phase of the ulcer problem obviously is needed but the most effective approach is not apparent. Histochemical studies of the stomach and duodenum might be informative in this connection. Knowledge in this field is in the developmental stage and new technics are constantly being developed. Although ulcer-bearing tissue would be readily available for this purpose, analysis of the "ulcer-prone"

stomach or duodenum, for the purpose of studying possible aberrations from normal before development of the ulcer, would appear virtually impossible.

OTHER THEORIES OF ULCER FORMATION

Gastritis. All types of gastritis are demonstrable gastroscopically in patients with peptic ulcer.[224–226] In many patients there is no visible inflammation. Hypertrophic gastritis is more common in duodenal ulcer; atrophy is more frequent in gastric ulcer. Konjetzny consistently found antral gastritis and erosions and no evidence of local vascular injury in stomachs resected for peptic ulcer and concluded that ulcer developed on the basis of an antecedent erosive gastritis; gastritis, duodenitis and ulcer thus represented stages of the same process. Experimentally, the oral administration of cinchophen produces an acute erosive gastritis in dogs, progressing to multiple acute ulcerations and finally to one chronic ulcer.[227] Gastroscopic evidence, on the other hand, is not in accord with the gastritic theory of ulcer formation; gastritis is not found in approximately one-third of ulcer patients; antral gastritis is rarely noted gastroscopically. Although erosions and acute superficial ulcerations occur in gastritis, we have not thus far observed gastroscopically the transition from gastritis to typical chronic gastric ulcer. On the other hand-jejunal ulcer has developed after postoperative erosive jejunitis, a sequence of events attribut, able to the action of acid gastric juice. While final conclusions are unwarranted, the present evidence suggests that ulcer usually does not develop as a direct consequence of gastritis; both may arise from acid-pepsin digestion.

Infection. There is no satisfactory evidence that foci of infection play a significant role in human peptic ulcer. Recurrences often are associated chronologically with upper respiratory infections but a significant unequivocal relationship between the two has not been established. Respiratory illnesses precipitate the recurrence of many, apparently unrelated chronic diseases.

Allergy. Allergic reactions can be induced experimentally in the mucous membrane of the stomach and elsewhere in the digestive tract.[228–230] These lesions heal rapidly and do not progress to chronic ulceration. There is no convincing objective evidence that allergy causes chronic peptic ulcer in man.

Nutritional Deficiency. The high incidence of peptic ulcer in certain areas of the world with inadequate supplies of food has been attributed to nutritional deficiency.[231,232] Histologic studies in one group of patients from South India demonstrated gastritis, duodenitis and degeneration of Auerbach's plexus in stomachs resected for peptic ulcer. Similar lesions were found also in the stomachs of patients in whom no ulcer was demonstrable at operation. Furthermore, the incidence of peptic ulcer does not seem excessive in other regions of the globe with equally poor diets. Acute gastric ulcers may develop in animals fed protein-deficient diets.[233] However, there is no acceptable evidence that hypoproteinemia is of fundamental importance in the pathogenesis of the human disease. Nutritional deficiency might contribute to the development of peptic ulcer, presumably by decreasing the resistance of the mucosa to acid digestion. However, protein deficiency is not usually demonstrable in uncomplicated peptic ulcer.[234]

Acute gastric ulcers may be produced in rats by feeding vitamin-deficient diets; these lesions do not resemble chronic peptic ulcer. Specific vitamin deficiencies have not been established as a cause of human peptic ulcer. The vitamin deficiencies reported in some patients with peptic ulcer[235–237] are secondary to poor dietary intakes.

"*Constitutional Susceptibility.*" The known occurrence of peptic ulcer in only approximately 10 per cent of the population during a life time has suggested the possibility of a "constitutional susceptibility." The nature of this susceptibility is uncertain; presumably it would include a predisposition to gastric hypersecretion, vasomotor disturbances, or perhaps hyper-reactivity of the digestive tract to emotional stimuli. Although no satisfactory evidence for this concept has come to our attention, future study might conceivably disclose factors increasing the tendency to the disease in some people. It is perhaps noteworthy in this connection that peptic ulcer occurs in all regions of the earth, among all peoples for whom accurate information is available, among persons of diverse occupation and among individuals with varying bodily habitus. The survey by Doll and Jones[238] suggested a positive correlation between "stressful" occupations and duodenal ulcer, a decreased incidence of ulcer among agricultural workers and a greater frequency of gastric ulcer

among people of poor economic status. The implications of these observations require further study.

Heredity. The high incidence of peptic ulcer in some families[239–241] and its presence in identical[242–244] twins raises the question of hereditary predisposition.[245–247] There can be little doubt that the familial incidence occasionally is very striking; such instances, however, appear to be the exception rather than the rule.[248] Bonarino and Nasio[249] could not elicit a familial predisposition in the localization of peptic ulcer. Riecker suggested the possible inheritance of a personality type or pattern of reactivity to emotional stress. Perhaps the emphasis should be directed to environmental factors and to "hereditary habits" rather than hereditary tendencies.[250]

Sex Differences—Hormones. Peptic ulcer is uncommon during childhood although recent studies indicate a higher frequency than had been realized.[251] Children secrete adequate quantities of acid and pepsin;[252–254] in the presence of duodenal ulcer the output of acid may be excessive. Necheles et al.[255] reported a male preponderance of 3:1 among twenty children of the ages one to thirteen with duodenal ulcer. According to most observers,[256,257] however, there is no significant sex difference in the incidence of peptic ulcer prior to the age of fourteen. After puberty the frequency of peptic ulcer rises in both sexes but the increase is much greater in men; after the menopause the incidence of peptic ulcer in women rises further. This sex difference has not been explained; speculation has centered about increased susceptibility and greater exposure to environmental factors. The higher gastric secretion in man, greater incidence in males and the apparent infrequency of active peptic ulcer during pregnancy[258] has suggested a relationship between gastric secretion, peptic ulcer and the sex hormones. The beneficial effect of pregnancy on ulcer also has not been clarified; the more frequent use of x-rays in the examination of pregnant women with digestive symptoms might disclose a higher incidence of peptic ulcer than had been suspected. If true, the beneficial action of pregnancy may be related to decreased gastric acidity or to improved resistance of the gastroduodenal mucosa to acid. Preliminary studies indicate that proprietary preparations of estrogens, progesterone, gonadotropins and testosterone propionate do not significantly inhibit gastric secretion in patients with duodenal ulcer.[259]

The possibility of an "anti-ulcer" substance promoting healing of the ulcer crater, apart from any effect on gastric acidity, has been suggested on the basis of various observations, including the prolonged absence of ulceration after the administration of enterogastrone in dogs subjected to the Mann-Williamson operation. According to Sandweiss and his associates, the urine of pregnant and non-pregnant women contains a substance capable of facilitating the healing of Mann-Williamson ulcers in dogs, without significant change in gastric acidity.[260] This protective factor apparently is not present in the urine of ulcer patients. The nature of this "protective" substance, its source and mode of production are not known. Additional studies of this problem would appear desirable.

All the endocrine glands have been implicated in the pathogenesis of peptic ulcer. The enormous literature on this subject is reviewed elsewhere.[261,262] Ulcerations have been induced experimentally by procedures inducing adrenal and thyroid-parathyroid insufficiency. The relationship of these observations to chronic peptic ulcer remains to be determined; much of the information available on the subject seems inconclusive. The role of the adrenal cortex and adrenal steroids has been discussed earlier.

MECHANISM OF ULCER PAIN

The pain of peptic ulcer is caused primarily by free hydrochloric acid.[263,264] The acid produces a chemical inflammation with vascular engorgement and edema, lowering the pain threshold of the nerve endings in the base and edges of the ulcer. The pain is a true visceral sensation; it arises directly at the site of the lesion, not in some distal part of the stomach or through any reflex mechanism. Acid gastric juice is the normal stimulus to the pain mechanism. Kymographic and roentgen studies indicate that ulcer pain is not dependent upon hyperperistalsis, generalized contraction of the stomach, distention of the antrum or rise in intragastric pressure. When the ulcer is sufficiently sensitive, however, mechanical factors such as peristalsis and spasm may evoke pain.

Ulcer distress occurs only when the gastric content is acid. The level of acidity necessary to evoke pain varies among individuals, in the same patient at different times and with the location of the ulcer. The level is usually

highest in duodenal ulcer (pH 1.5) and lowest in jejunal ulcer (pH 2.5). The concentration of acid at the time of distress need not be excessive. The occurrence of pain, therefore, is dependent upon an inflamed ulcer crater and lower pain threshold. In the presence of a sensitive pain mechanism distress may be induced by the instillation of physiologic concentrations of acid into the stomach, the administration of acid gastric juice, or by the stimulation of acid secretion with histamine. The pain is relieved promptly by gastric aspiration, neutralization of acid with alkali or food or inhibition of acid with antisecretory drugs and in duodenal ulcer by inhibition of gastric emptying. Anticholinergic compounds do not block or "desensitize" the pain mechanism.[265] The absence of pain or its relief after administration of these compounds in duodenal ulcer is attributable to delay in gastric emptying with consequent rise of the pH on the surface of the ulcer; the instillation of hydrochloric acid directly into the duodenal bulb promptly evokes pain in a sensitive ulcer, despite the injection of anti-cholinergic drugs.

Pain sensitivity disappears rapidly, especially during antacid and antisecretory therapy; presumably the acute inflammation subsides and granulation tissue covers the nerve endings. The mild distress or absence of pain in occasional patients preceding perforation or massive hemorrhage is not readily explained, except on the basis of low sensitivity and a high pain threshold. Ulcer pain is transmitted to the brain via the splanchnic nerves as is shown by the fact that pain can be reproduced immediately after complete vagotomy in sensitive ulcers by the gastric instillation of hydrochloric acid[266] and further by the fact that splanchnicectomy apparently does abolish ulcer pain.[267]

THERAPY—PHYSIOLOGIC PRINCIPLES

Tissue Resistance. The purpose of therapy in peptic ulcer is protection of the mucosa from the digestive action of acid gastric juice.[268] This objective might be accomplished by increasing the resistance of the mucosa or by permanently inhibiting the secretion of acid. There is no known direct method for improving the tissue defenses in peptic ulcer, desirable as this may be; theoretically this might be facilitated indirectly by maintaining the health of the patient, avoidance of gastric irritants and by relief from emotional stress. The clinical value of "uroanthelone"[260] and extracts of pregnant mares' urine remains to be established. Attempts to improve tissue resistance by the administration of extracts of animal stomach, duodenum,[269-271] colon and various endocrine glands have been unimpressive;[272-274] furthermore, there is no physiologic basis for the oral use of such extracts. Evaluation of the effects of various extracts of animal stomach and intestine, as well as urinary extracts, in peptic ulcer is seriously handicapped by lack of knowledge of their chemical composition, biologic behavior and mode of action. Further fundamental study of this problem would appear indicated.

Neutralization and Inhibition of Acid Secretion. The complete and permanent elimination of acid secretion would eliminate the ulcer problem, regardless of tissue resistance and other factors possibly implicated in the pathogenesis of the disease. Unfortunately, there continues to be no technic, medical or surgical, with the exception of total gastrectomy, that regularly produces complete and permanent anacidity; hence, there is no procedure, pharmacologic or operative, that *per se* regularly leads to cure. Present therapy, consequently, continues to be concerned with effective neutralization or inhibition of free acid and pepsin activity in the gastric content.

None of the available antacids completely neutralizes gastric acidity in peptic ulcer for prolonged periods, partly because of inadequate neutralizing properties, chiefly because of rapid emptying from the stomach.[275] The most effective compound, in our experience, is calcium carbonate, administered in doses of 2.0 or 4.0 gm. hourly; it does not cause alkalosis; its constipating effect is readily controlled with magnesium carbonate. Aluminum and magnesium salts and resins neutralize gastric acidity to a lesser degree. Detergents and mucin are not effective in man. Antacids neutralize acid only during the period of administration. The excessive nocturnal gastric secretion in duodenal ulcer is not controlled unless therapy is continued during the night, either with antacids administered orally or in the form of a continuous intragastric drip. The effectiveness of antacid therapy thus depends upon prolonged use. This regimen is not acceptable to many patients. Considerable effort, therefore, is being directed to the development of compounds inhibiting gastric secretion after parenteral or

preferably oral administration. Anti-histaminic drugs, sex hormones and currently available concentrates of enterogastrone[276] do not significantly depress gastric secretion in man.

Anti-cholinergic compounds have yielded more promising results. Atropine decreases the output of acid in approximately one-fourth of patients with duodenal ulcer; however, toxic effects are common. The chief advantage of atropine in ulcer therapy may be to delay gastric emptying, thereby facilitating more effective neutralization by antacids. The value of synthetic atropine-like compounds seems doubtful. Tetraethylammonium salts given parenterally and hexamethonium compounds by mouth may decrease gastric secretion but the side effects often are disturbing. Banthine® inhibits acid production temporarily when given parenterally; its antisecretory effect after oral use is far less impressive; side effects are common. The action of prantal® is similar although it seems to be better tolerated. More potent antisecretory compounds have been made available recently.[277] Single doses of several of these drugs have induced complete anacidity in patients with duodenal ulcer for periods of four to eight hours; however, side effects are pronounced. The goal of prolonged, effective inhibition of acid secretion without disturbing reactions remains to be achieved; it may be unattainable. On the other hand, the progress made thus far suggests the possible development of clinically tolerable and potent antisecretory drugs. Such compounds would improve the medical management of peptic ulcer by suppressing gastric secretion, permitting a more practical and yet more effective program of neutralization with antacids than has been possible heretofore.

Gastric Irradiation. Acid secretion in peptic ulcer also may be suppressed by roentgen-irradiation of the acid-secreting portions of the stomach with small quantities of x-ray[278] or radium.[279] The development of complete anacidity is followed invariably by complete healing of the ulcer and by no recurrence for the duration of anacidity. The extent of the decrease in secretion and its duration are variable and unpredictable. The recurrence of ulcer always is preceded by the reappearance of hydrochloric acid. The clinical course of some patients with duodenal ulcer seems less severe after gastric irradiation than before; the improvement may be related to a change from the continuous acid secretion preceding therapy to the intermittent production of acid after irradiation.

Evaluation of Therapy. Evaluation of these and other therapeutic measures in terms of the immediate subjective response of the ulcer patient is treacherous because the symptoms frequently subside for psychotherapeutic and nonspecific reasons, at least temporarily, with any program including enthusiastically administered medication and closer personal supervision. The efficacy of treatment in peptic ulcer requires careful study for long periods of time, with adequate controls, and in relation to the recurrences and life history of the individual patient.

Healing. All ulcers, gastric and duodenal, acute and chronic, possess a natural tendency to healing. Many uncomplicated lesions heal in spite of the presence of acid gastric content, as shown by the "spontaneous" remissions of the disease and by the healed scars found at x-ray and at autopsy; however, the healing of peptic ulcer is much more rapid when the lesion is protected from the action of acid gastric juice.[280,281] The time required for complete healing varies, averaging approximately six to eight weeks;[282,283] chronic benign gastric ulcer may persist for longer periods. "Intractability" is attributable chiefly to the inadequate control of gastric secretion.[284,285] This may result from inadequately prescribed therapy, failure of the patient to maintain treatment, emotional problems, or from complications, especially stenosis and gastric retention.

Recurrences. Recurrences are common with almost any type of therapy, medical or surgical, that does not permanently decrease or eliminate the free acid. The recurrent lesion may be the old ulcer undergoing an acute exacerbation, a new lesion at the same site, or an entirely new ulcer. It has been estimated that the average ulcer patient experiences one recurrence every two years, although he is free of symptoms most of the time.[286] Althausen's[287] summary of ten recent studies indicates that 46 to 93 per cent of patients experience one or more recurrences within five years. It is our impression that the record is better in patients maintained indefinitely on adequate medical management; however, many more carefully documented life history studies are needed to evaluate this important problem. The recurrences are not correlated consistently with any single cause. The factors recognized and emphasized most often are: physical and mental fatigue, emotional

stress, dietary indiscretions and perhaps infections of the upper respiratory tract. These are common stresses in life, precipitating the recurrence of many chronic diseases. Actually, the so-called spontaneous remissions and relapses of peptic ulcer have never been explained satisfactorily.

The role of emotional conflict in the recurrences of ulcer is no less difficult to evaluate than in the pathogenesis of the disease. In the series of patients' studies by Flood,[288] worry, fatigue, anxiety and insecurity were the commonest precipitating factors. However, relapses equally often were not obviously associated with these emotional conflicts. Furthermore, patients free of ulcer distress for long periods of time were subjected to emotional trauma and feelings of insecurity during the symptom-free intervals.

There are no specific measures completely protective against recurrences, except the production of permanent anacidity. The prevention of peptic ulcer probably will be facilitated by a comprehensive program comprising (1) education of the patient as to the nature of the ulcer, the principles of treatment and its objectives; (2) resolution of emotional problems, if possible, with re-orientation to a "life of moderation"; (3) use of a bland diet and avoidance of gastric irritants; (4) a practical but effective program of acid neutralization and inhibition; (5) adequate sleep and rest and (6) proper care of respiratory infections and other intercurrent illnesses. This general program is applicable obviously not only to the prevention of the recurrence but, indeed, constitutes the medical treatment of the disease itself.

SURGERY

Surgical treatment is necessary in approximately 10 to 15 per cent of patients. The principal procedures are posterior gastroenterostomy, gastric resection, and vagotomy and gastroenterostomy.[289,290] These operations do not influence tissue resistance; hence, their success depends chiefly upon the degree to which the output of acid is decreased.

Gastroenterostomy facilitates the healing of duodenal ulcer by diverting the acid gastric content from the ulcer area. The secretion of acid is unchanged, except perhaps for the neutralization resulting from reflux of intestinal content. Consequently, the excessive outputs of acid acting upon a more susceptible jejunal mucosa frequently cause the complication of jejunal ulcer.

Complete vagotomy, dividing the vagi at the lower end of the esophagus, profoundly diminishes the excessive output of acid in duodenal ulcer. The decreased response to sham feeding and insulin hypoglycemia indicates interruption of the pathway for stimuli of central origin. The lowered reactivity of the parietal cells to direct stimulation with histamine suggests interruption of at least one pathway for stimuli of peripheral origin. Vagotomy and posterior gastroenterostomy have been utilized most often in the surgical management of stenosing duodenal ulcer and jejunal ulcer. The procedure is not appropriate physiologically in gastric ulcer because the output of acid is less than normal and vagotomy does not further depress the already low gastric secretion.

Gastric resection is highly effective in the surgical treatment of gastric ulcer; jejunal ulcer is very infrequent because of the small output of hydrochloric acid. The value of gastric resection in duodenal ulcer is proportional to the reduction in gastric secretory potential. Adequate resection for this purpose requires removal of most of the parietal cell mass in the body of the stomach; resection of the antrum does not necessarily reduce the hypersecretion.

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Research Society Abstracts

Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SIXTH ANNUAL MEETING, ATLANTA, GEORGIA, JANUARY 19, 1952

THE CELL MEMBRANE DEFECT IN ACUTE RHEUMATIC FEVER. *J. K. Aikawa.* (From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.)

Serial determinations of the radiosodium (Na_{24}) space were made in two patients with acute rheumatic fever treated with salicylates. The early course of the disease is characterized by polyarthritis with serous effusion suggesting a change in permeability of cell membranes. A 15 year old boy with a temperature of 102.8°F. had a Na_{24} space of 20,436 ml. (46.3 per cent of body weight). After fourteen days of oral therapy with 3.6 gm. acetylsalicylic acid daily the body weight was unchanged but Na_{24} space was 14,389 ml. (32.7 per cent of body weight). Therapy was discontinued and the space increased but with resumption of therapy decreased a second time to 29.2 per cent. In a sixteen year old boy a space of 18,818 ml. (36.8 per cent) rose to 21,044 ml. (41.9 per cent) but on 3.6 gm. acetylsalicylic acid dropped to 17,520 ml. (33.7 per cent). Initial sedimentation rates of 32 and 34 mm./hr., respectively, dropped to 9 in each case. Generalized clinical edema was not present although values greater than 30 per cent have not been encountered previously without edema. Intracellular fluid might migrate to the extracellular compartment in the acute phase but a shift of 6 L. should produce pitting. More probably the permeability of cells, especially of connective tissue, is increased to sodium; this physiologic defect is suppressed by salicylates.

EXCHANGEABLE POTASSIUM CONTENT OF NORMAL WOMEN. *J. K. Aikawa, G. T. Harrell and (by invitation) B. Eisenberg.* (From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.)

The exchangeable potassium content of the body (K_e) may be estimated after the injection of a tracer amount of radioactive isotopic K_{42}. Previous studies have found a mean value of 46.3 mEq./kg. in a homogeneous group of thirty young men. Because of differences in physical characteristics and endocrine function in women, a group of twenty healthy young women was similarly studied. A mean value of 31.5 mEq./kg. was found; the range of variation was less than in men. No correlation was found between K_e and urinary creatinine excretion in women, contrary to the findings in men. The lower K_e in women is apparently due to their relatively greater fat content and variability in the proportion of muscle to other tissues. In women alterations in K_e should be studied by serial determinations in the same individual.

BODY POTASSIUM LOSS DURING THERAPY WITH ACTH AND CORTISONE. *J. K. Aikawa and (by invitation) J. H. Felts.* (From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.)

Serial determinations of the exchangeable potassium content of the body (K_e) were made by a radioactive isotopic (K_{42}) technic in four patients. A sixty-five year old woman with arthritis received intravenously 20 mg. ACTH daily with 3 gm. KCl orally. In seven days the K_e/wt. fell from 34.8 to 25.8 mEq./kg. (normal for women 31.5 mEq./kg.). A twenty-five year old man received cortisone in varying doses for seven months; sodium was not restricted nor was a potassium supplement given. He gained 45 pounds and developed signs of Cushing's syndrome. The K_e/wt. of 26.7 rose to 34.9 mEq./kg. in fourteen days after hormones were stopped (normal for men 46.3 mEq./kg.). Another man given 100 mg. cortisone orally for five months had K_e/wt. of 30.2 mEq./kg. A man aged fifty-six with exfoliative dermatitis received 50 mg. cortisone orally for eight months. Sodium intake was restricted (<2 gm. daily) and KCl was given (1 gm. daily). The K_e/wt. of 40.5 mEq./kg. fell to 36.9 mEq./kg. as therapy was withdrawn. The potential magni-

tude of the potassium deficit which may develop (511 mEq. in Case 1) is greater than might be anticipated from balance studies. Proper therapy prevents deficits. Reduction of less than 30 per cent in K_e was not accompanied by clinical symptoms or signs of deficiency.

ACTH IN PRIMARY REFRACTORY ANEMIA: *W. Bruce Barton, D. A. Howell (by invitation), and R. W. Rundles.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

Five patients with primary refractory anemia present for periods of four weeks to four years were treated with ACTH (corticotropin®). All five patients had leucopenia and anemia requiring blood transfusions and four had thrombocytopenia with bleeding. In three patients an etiologic agent was not discovered. Sulfonamides had been used by one patient; another had been overtreated with triethylene melamine.

ACTH was given in full doses for eleven to twenty days. There was slight or no increase in the number of formed elements in the circulating blood. Of the three patients with idiopathic pancytopenia, one of whom had a normally cellular marrow, none was benefited and one died from protracted hemorrhage. Recovery occurred in the patient in whom sulfonamides appeared to be the etiologic agent, in spite of agranulocytosis, leucopenia as low as 550, virtually acellular marrow and heavy bacteremia. The severe marrow depression, persisting for three weeks after suspension of TEM therapy, subsided slowly after three weeks of ACTH.

Patients with chronic marrow depression or aplasia show little immediate hematologic response to ACTH and no long term benefit. Those with acute marrow injury in whom spontaneous recovery is possible may be helped by ACTH.

DEMONSTRATION THAT INSULIN IS FIXED LOCALLY WHEN INJECTED INTO THE FEMORAL ARTERY IN HUMANS. *David M. Bell, Thomas Burns, James Schieve (introduced by Eugene A. Stead, Jr.)* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

Small doses of insulin (1/80 unit per kg.) produced definite but small asymptomatic depression of the blood sugar. Two groups of ten hospital patients were compared in their response to intravenous and intra-arterial insulin injection. Blood samples were collected from the femoral artery and vein of the leg. Following intravenous injection it was seen that the blood sugar level fell, although simultaneous femoral venous and arterial blood samples contained essentially the same sugar concentration. However, following femoral artery injection of insulin there was an increase in the arteriovenous difference during the time of fall. A further experiment using seven healthy students was conducted in which insulin was given into the femoral artery and blood taken from the same artery and from the femoral vein of each leg. There was an increase in arteriovenous sugar difference across the injected leg with essentially no measurable difference across the control leg during the time of fall of arterial concentration. At fifteen minutes (the point of maximum arterial drop) there was a statistically significant difference in arteriovenous differences in both experiments. It is suggested that insulin injected into a femoral artery is fixed in the extremity and that it increases the glucose removal from that extremity without a corresponding increase in the opposite extremity.

STUDY OF THE SODIUM, CHLORIDE AND POTASSIUM CONTENT OF THERMAL SWEAT OF MAN COLLECTED FROM SMALL ISOLATED AREAS. *G. S. Berenson (by invitation) and G. E. Burch.* (From the Department of Medicine, Tulane University of Louisiana School of Medicine, New Orleans, La.)

Content of Na, Cl, K and water in thermal sweat was observed simultaneously in sixteen adults convalescing from various illnesses. All collectable sweat was obtained (over periods of approximately one hour) by aspiration from cleaned skin enclosed within plastic cups. The mean rate of sweating was 0.170 cc. (range 0.104–0.292)/10 cm^2 skin surface area/10 minutes for thirteen males and 0.070 cc. (range 0.061–0.087) for three female subjects. Concentration-time course curves revealed that Na and Cl increased concordantly toward a maximum concentration, the mean Cl/Na ratio being 0.877 (0.647–1.318). Potassium concentrations, initially high, decreased to almost constant values. The range in concentration of Na and Cl for all subjects was approximately 10–100 mEq./L. whereas that of K was 4.5 to 18.5 mEq./L. Moment to moment and subject variations were conspicuous. No difference was found for opposite forearms, but variations in concentration of electrolytes were obtained for five different sites (forehead, forearm, axilla, epigastrium and thigh). Mean values of maxi-

mum concentrations of Na and Cl noted for the thigh were 58.2 per cent and 48.1 per cent of respective maximum concentrations for axillary sweat. These experiments indicate need for further studies concerning the mechanism of sweat formation and standard conditions for its induction and collection.

SPONTANEOUS VARIATIONS IN THE RATE OF OUTPUT OF GLUCOSE BY THE LIVER IN NORMAL MAN. *Philip K. Bondy.* (From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.)

The rate of release of glucose by the human liver has been assumed in the past to be relatively constant under basal conditions. The correctness of this assumption was investigated by estimating the splanchnic glucose balance in normal human beings under basal conditions by the liver catheter technic over periods of time from five to forty-five minutes at intervals of thirty seconds to ten minutes. The output of glucose is not constant but varies widely and spontaneously to such a degree that in no case was the mean glucose balance significantly different from zero. The use of constant sampling technics fails to alter the situation and introduces additional errors. The estimation of long term splanchnic glucose balances by the use of the catheter is, therefore, a highly inaccurate and untrustworthy technic. The results obtained reflect only the balance at the moment of sampling. Conclusions drawn from these "instantaneous" balances should not be applied to over-all metabolic patterns purporting to represent the state of affairs over prolonged periods.

PHYSIOLOGIC TESTS USED IN EVALUATING MITRAL STENOSIS IN PATIENTS FOR VALVULOTOMY. *Don W. Chapman and (by invitation) Ray H. Skaggs, Ira T. Johnson, Lewis C. Mills and Denton A. Cooley.* (From the Departments of Medicine and Surgery, Baylor University College of Medicine, Houston, Tex.)

With the advent of successful mitral valvulotomies more careful methods of evaluating suitable candidates for surgery have become necessary. In this series preoperative catheterization determinations and postoperative studies, when available, will be presented.

Twenty patients with mitral stenosis as a predominating lesion were studied. Cardiac outputs were determined by the Fick principle in the resting and exercise states, and in some in the post-exercise period. Pressure readings were recorded from the so-called "pulmonary capillaries," pulmonary artery, right ventricle, right atrium and systemic arteries by means of an electrical manometer. Resting cardiac outputs were found to be reduced and very little or no increase in output was noted with exercise in patients with tight mitral stenosis. Resting pulmonary capillary pressures were found to be elevated in the majority and became excessively elevated with exercise as did the corresponding pulmonary arterial and right ventricular pressures. Pulmonary artery and arteriolar resistances were increased in many. Valvulotomies were performed thirteen times in this series with no mortality. In those restudied, cardiac outputs were found to be relatively unchanged but pulmonary capillary pressures and pulmonary arteriolar resistances were reduced. An increase in valvular size was noted postoperatively using Gorlin's formula.

EVALUATION OF THE DYE DILUTION METHOD OF MEASURING CARDIAC OUTPUT AND SO-CALLED PULMONARY BLOOD VOLUME. *Joseph T. Doyle, Joseph S. Wilson (by invitation) and James V. Warren.* (From the Departments of Medicine and Physiology, Emory University School of Medicine, Atlanta, Ga.)

By injecting T-1824 into a cardiac catheter and collecting arterial blood during first circulation of the dye, one can measure mean circulation time (MCT), cardiac output (CO) and so-called pulmonary blood volume (PBV), the volume between catheter and arterial needle. Approximately 300 such measurements permit the following conclusions.

CO measured by the dye and Fick methods correlate satisfactorily, except with extremely low CO, intracardiac shunts and free aortic regurgitation. The dye method is otherwise adequately reproducible. Normal resting PBV is 634 ± 122 cc./M^2 and is not correlated with pulmonary arterial pressure or stroke volume. Artificial expansion or reduction of general blood volume (GBV) does not alter the ratio PBV:GBV. In hypokinetic heart failure PBV is large while in hyperkinetic failure PBV is normal. In both the normal ratio PBV:GBV is maintained at about 25 per cent. Mitral stenosis (MCT prolonged; PBV and PBV:GBV large) and tricuspid insufficiency (MCT slightly prolonged; PBV and PBV:GBV relatively small) alone show significant contrast. Tilting and venous pooling of blood produce a statistically equivocal reduction in measured PBV.

It is concluded that the dye measurement of CO is useful but the estimation of PBV is relatively insensitive in quantitating small but physiologically important variations.

CHLORAMPHENICOL IN THE TREATMENT OF PNEUMONIA: A COMPARISON WITH PENICILLIN. *W. C. Ebeling, R. T. Parker, R. C. Hagan, J. E. Cohen and V. D. Bennett (introduced by Theodore E. Woodward).* (From the Section of Infectious Diseases, Department of Medicine, School of Medicine, University of Maryland, Baltimore, Md.)

The results of therapy in thirty-four patients receiving chloramphenicol® and thirty-two patients given penicillin are presented. D. pneumoniae were isolated from the upper respiratory tract of each case and pneumococcal bacteremia occurred in approximately 15 per cent. In order to define the etiologic significance of certain viral agents the following tests were performed: complement fixation for Q fever and psittacosis, the agglutination inhibition test for influenza A, B, and A′, the cold hemagglutination and streptococcus MG agglutination tests. Approximately 10 per cent showed evidence of a second factor as a cause of the disease other than D. pneumoniae isolated from the sputum or blood stream.

Mean values for the day of disease on which treatment began were chloramphenicol 3.5 and penicillin 5.0. After twenty-four hours of therapy 79 per cent of the chloramphenicol and 75 per cent of the penicillin-treated patients had normal temperatures. The incidence of fatality (one case in each group), bacteremia and complications were similar in both groups. Mean values for the duration of therapy and total dosage of penicillin and chloramphenicol were 9.7 days and 3.2 million units, and 7.6 days and 24.1 gm., respectively.

STUDIES ON THE METABOLIC RESPONSE TO INJURY: ROLE OF THE ADRENAL CORTEX IN CARBOHYDRATE METABOLISM DURING ILLNESS. *Frank L. Engel and Thomas W. Burns (by invitation).* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

Stemming from the original views of Selye, the concept is widely held that the metabolic response to injury is a direct consequence of hypersecretion of adrenal cortical steroids. However, studies by Ingle and from this laboratory have shown that while adrenal hormone is necessary for the metabolic response to injury, it is not responsible for it. On the basis of extensive studies with animals the concept has been further developed in this laboratory that adrenal hormone in amounts beyond that necessary to sustain the response to injury sensitizes the organism to overrespond to damage.

In a series of 200 glucose, glucose-insulin and insulin tolerance tests on eighty-seven normal and forty ill subjects untreated and receiving 200 to 400 mg. of oral cortisone four hours before testing or 200 mg. daily for seven days, it was found that (1) the response of normal subjects to these tests was in general significantly different from those of ill individuals; (2) the response of normal subjects given cortisone was significantly different from ill subjects; and (3) ill subjects receiving cortisone exhibited strikingly greater impairment in carbohydrate tolerance than did normal subjects similarly treated with cortisone. These results support the above interpretation of the relation of the adrenal cortex to the metabolic response to injury.

SIMPLIFIED MANAGEMENT OF HYPERTENSIVE TOXEMIAS OF PREGNANCY USING A PURIFIED EXTRACT OF VERATRUM VIRIDE. *Frank A. Finnerty, Jr., (introduced by H. H. Hussey).* (From the Georgetown University Medical Division, Gallinger Municipal Hospital, Washington, D. C.)

Aqueous injectable vergitryl® (a purified extract of Veratrum viride containing known concentrations of the hypotensive ester-alkaloids germitrine and germidine) was used as the principal agent in therapy of 122 cases of hypertensive toxemias of pregnancy. In the eight cases of convulsing toxemia intravenous administration of vergitryl gave excellent results in four, good results in two and fair results in one. The finding that 0.5 mg. of vergitryl by the intramuscular route produced uniform reduction in arterial pressure with absence of severe hypotensive reactions and oliguria, permitted the adoption of a simple and safe treatment schedule for the non-convulsive toxemias. In the 114 cases of non-convulsive toxemias there were excellent results in ninety-two, good results in eighteen, fair results in three and a poor result in only one. There were no maternal deaths and only two fetal deaths. Since tolerance did not occur, therapy could be continued for as long as ten days in three patients. Accidental overdosage of four times the effective dose in two cases produced only transient

toxicity, attesting to the drug's wide margin of safety. Vomiting was the only toxic manifestation, occurring in 16 per cent of cases. It was readily controlled by pentobarbital sodium administered intravenously. Because of the uniform and controlled response and because large doses of sedatives were unnecessary, the patients remained alert, ate well and did not require observation.

ENDOCRINE FACTORS IN CONGESTIVE HEART FAILURE. *Francis W. Fitzhugh, Jr., Ralph A. Huie (by invitation) and Arthur J. Merrill.* (From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.)

Sweat sodium data previously reported from this laboratory have indicated increased mineral corticoid activity of the adrenal cortex in congestive heart failure. The present report deals with further studies to elucidate the endocrine factors in congestive heart failure.

Using a bioassay method employing human subjects as described by Brun, an attempt was made to demonstrate the presence of excessive circulating antidiuretic hormone in the blood of patients with chronic congestive heart failure. Three hundred to 400 ml. of blood were drawn from the cardiac patients and immediately transfused into normal recipients. No decreases in renal plasma flow, glomerular filtration rate, urine volume or sodium and potassium excretion were observed.

It has been repeatedly demonstrated that hypofunction of the anterior pituitary, adrenal cortex or thyroid results in marked diminution in renal plasma flow and glomerular filtration rate. ACTH, cortisone, desoxycorticosterone acetate and thyroid extract were administered in large doses to patients with chronic congestive heart failure for periods of at least four days. No significant change occurred in the markedly depressed renal clearances of these patients.

HEMODYNAMIC ALTERATIONS IN ACUTE MYOCARDIAL INFARCTION: MECHANISM OF CARDIOGENIC "SHOCK." *Edward D. Freis and (by invitation) Harold W. Schnaper and Robert L. Johnson.* (From the Cardiovascular Research Laboratory, Department of Medicine, Georgetown University Medical Center and the Veterans Administration Hospital, Washington, D. C.)

Recent evidence indicates that values for cardiac output obtained with the Hamilton dye injection technic are in essential agreement with those attained using the intravenous catheterization (Fick) method. The Hamilton technic was adapted for use at the bedside in patients with recent myocardial infarctions and the results compared to a group of controls.

The hemodynamic abnormalities could be divided into three groups which correlated with the severity of the infarction as estimated clinically. The first group (severe infarctions with cardiogenic "shock") exhibited marked reductions of cardiac output, especially stroke volume, increases in total peripheral resistance, heart rate, central venous pressure and average circulation time, slight and possibly insignificant reductions of total blood volume and essentially normal central blood volumes. The second group (mild cases) did not exhibit significant abnormalities while the third group was intermediate both in clinical severity and in regard to hemodynamic alterations.

These observations in patients are in agreement with the animal experiments of Wiggers and suggest that the initial change after an extensive infarction is a reduction of stroke volume secondary to the myocardial insult. This is followed by intense compensatory vasoconstriction and tachycardia producing a clinical picture superficially resembling shock but differing from it fundamentally in that central blood volume is essentially normal. This vasoconstriction and markedly reduced stroke volume, if sufficiently prolonged, may result in a fluid retention syndrome which, in the presence of a defective myocardium, produces congestive heart failure as well as the shock-like state.

CORRELATION BETWEEN THE VASODILATION PRODUCED BY THORACIC OR LUMBAR SYMPATHECTOMY AND THE VASODILATION PREDICTED FROM THE EFFECTS OF BLOCKING DRUGS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE. *Harold D. Green.* (From the Department of Physiology and Pharmacology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.)

Temperature of digits or toes (sixteen patients) was recorded while extremities were exposed to a constant temperature of 20 to 22°C. Studies were made before and within twenty days after fourteen lumbar and five thoracic sympathectomies. In preoperative study the patient was cooled for 20 minutes, then the torso was heated for 30 minutes. While continuing heating, an intravenous infusion of 15 to 20 mg./kg. of etamon® (thirteen subjects), 2 mg./kg. of priscoline® (ten subjects) or 0.5 mg./kg. of

regitine® (five subjects) dissolved in 250 ml. of saline was given over 30 minutes. Two or more drugs were used on seven patients studied. Among nineteen extremities tested, four upper and four lower showed absence of occlusive disease (max. skin temperatures 10 to 15°C. above room temperature); five upper and one lower showed evidence of moderate occlusive disease (4 to 9°C. above room temperature); five lower had severe occlusive disease (0 to 3°C. above room temperature). In postoperative study the same procedure was repeated, omitting the drug. In all but one instance maximum temperature reached during infusion of etamon was within +4.0° and −2.0° of that obtained in postoperative study (mean deviation +2.5 and −1.3°C.). Priscoline was almost as accurate and occasionally more so. Regitine often gave skin temperatures significantly lower than those obtained postoperatively.

This method of testing with etamon and priscoline gives an excellent estimation of the vasodilation which may be expected from sympathectomy contemplated for relief of peripheral vascular disease.

PARASYMPATHOLYTIC EFFECTS OF PRANTAL IN ANIMALS AND MAN AND CLINICAL TRIAL IN THIRTY PATIENTS WITH PEPTIC ULCER. *Keith S. Grimson and (by invitation) Benjamin H. Flowe and C. Roy Rowe, Jr.* (From the Department of Surgery, Duke University School of Medicine, Durham, N. C.)

Prantal® (N, N-dimethyl-4-piperidylidene-1, 1-diphenylmethane methyl sulfate) administered parenterally to dogs blocks the cardiac slowing effect of vagal stimulation and slows the transit time of barium through the stomach and ileum. The drug does not effect significant change of blood pressure or alterations of responses to the carotid sinus and other reflexes or to the injection of epinephrine. In man 50 mg. intramuscularly consistently reduces the volume and acidity of gastric secretions obtained at fifteen-minute intervals, an effect persisting several hours. As As judged by gastrometric studies, fluctuations of intragastric pressure were markedly reduced or stopped for periods of about an hour. Parasympatholytic side effects, as dryness of the mouth and dilatation of the pupil, were minimal. One hundred or 200 mg. orally less consistently reduced the volume or acidity of secretions and only occasionally significantly reduced fluctuations of intragastric pressure. Continuing administration to ambulatory ulcer patients of usually 200 mg. every six or every four hours effected relief of symptoms. Frequently there was lessening of the abnormalities originally evident by gastroduodenal fluoroscopic and roentgenologic studies. The drug is well tolerated, there being minimal or no effects on vision and little or no dryness of the mouth or difficulty in voiding. Constipation occasionally occurs.

RELATIONSHIP OF STATIC BLOOD PRESSURE TO CARDIAC FAILURE. *Arthur C. Guyton.* (From the Department of Physiology and Biophysics, School of Medicine, University of Mississippi, University, Miss.)

The hearts of sixty-one intact dogs under pentobarbital anesthesia were fibrillated with electrical current applied through the chest wall. Pressures were recorded from the femoral artery and right auricle. Immediately following fibrillation the two pressures began approaching each other and came essentially to equilibrium in fifty seconds. This equilibrium pressure in normal dogs was found to average 11.2 mm. Hg, but it continued to rise a mm. or more for another minute, after which it fell gradually to a stationary level of 4.4 mm. Hg at fourteen minutes. Preliminary infusions, pressoreceptor denervation and administration of epinephrine increased this "static blood pressure" whereas anesthetization of the sympathetics greatly decreased it. Theoretically, capillary pressure also should have approached the static pressure level. This means that sudden failure of the heart must have caused the capillary blood pressure to fall from 22 - 25 mm. down to 11.2 mm. In other words, the falling arterial pressure affected capillary pressure more than did the rising venous pressure. With this fact in mind, it seems that back pressure from the heart in congestive failure cannot be the only, and perhaps not the most important, cause of high capillary pressure and tissue edema.

CEREBRAL CIRCULATION AND METABOLISM IN SICKLE CELL AND OTHER CHRONIC ANEMIAS: EFFECTS OF OXYGEN INHALATION. *Albert Heyman, John L. Patterson, Jr. and (by invitation) T. Whatley Duke.* (From the Departments of Medicine and Physiology, Emory University School of Medicine, and the Medical Service › Grady Memorial Hospital, Atlanta, Ga.)

The alterations in the cerebral circulation and metabolism were studied before and after inhalation of oxygen in ten patients with sickle cell anemia and eight patients with chronic anemia of other types.

The mean hemoglobin value in the patients with sickle cell anemia was 7.8 gm./100 cc. while that of the patients with anemia of other etiology was 6.5 gm./100 cc. The group with sickle cell anemia showed considerable elevation in cerebral blood flow (CBF) with a mean value of 72 cc./100 gm. brain/min., compared to the normal mean of 50 cc. The increase in CBF in the patients with other types of chronic anemia was less striking. The mean cerebral oxygen consumption (CMR O_2) in both groups of anemic patients was 2.4 cc./100 gm./min., a value significantly below the normal of 3.1 cc. Oxygen inhalation produced a decrease in CBF comparable to that found in control subjects. Following oxygen administration a number of patients with anemia exhibited an increase in CMR O_2 in contrast to the control subjects who showed little change in cerebral oxygen consumption.

The increase in CBF observed in chronic anemia is believed to be produced by a decrease in blood viscosity and by the vasodilator stimulus of a reduction in mean capillary and venous oxygen tension. It is apparent that the metabolism of the central nervous system suffers more profoundly in anemia than is generally appreciated.

EFFECT OF ADRENALECTOMY ON THE TRIPHENYL-TETRAZOLIUM-CHLORIDE (TTC) REDUCTASE ACTIVITY OF RAT TISSUES. *Cornelia Hosh-Ligeti and Yin Tang Hsu (introduced by Alfred Chanutin).* (From the Department of Pathology, University of Virginia School of Medicine, Charlottesville, Va.)

The effect of total and subtotal adrenalectomy on the reductase activity of tissues from Wistar rats was studied histologically and chemically by means of the enzymatic reduction of TTC. Endogenous and succinate reductions were estimated in kidney, heart and liver slices of 0.1 to 0.2 mm. thickness.

After incubation with 0.25 per cent TTC for one hour at 38°C. slices were examined histologically. The large crystals formed by reduced TTC distorted the tissue and rendered the localization of enzymes impossible. From other incubated sections the amount of acetone-extracted dye was determined spectrophotometrically. The activity of the tissue was expressed as μg. dye reduced per mg. dry weight. Succinic dehydrogenase was estimated both in hand-cut and frozen sections. The values with frozen sections were identical to those of hand-cut slices. The kidneys showed marked decrease of the endogenous reductase in totally but not in subtotally adrenalectomized rats. Decrease was observed after twenty-four hours and became more pronounced after longer intervals. It reached 25 per cent of the mean control value in twenty-four days. The succinic dehydrogenase seemed lower than that of controls. The decrease in endogenous and succinic reductase of heart and liver slices after adrenalectomy was not significant.

RELATIONSHIP BETWEEN CHOLINESTERASE ACTIVITY AND PERMEABILITY OF GUINEA PIG AURICLES TO SODIUM AND POTASSIUM. *William C. Holland (by invitation) and Margaret E. Greig.* (From the Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn.)

The effects of various substrates and inhibitors of acetyl cholinesterase on the permeability of guinea pig auricle to sodium and potassium has been investigated. Under optimum conditions for hydrolysis of acetyl choline or acetyl-β-methyl choline the greatest liberation of K from the muscle occurred. The K lost was replaced by Na benzoyl choline, which is not hydrolysed by the true cholinesterase and did not affect the release of K. Inhibitors of cholinesterase such as physostigmine or methylene blue partially or completely reversed the effect of acetyl choline, depending upon the concentration of substrate employed. Atropine, which inhibits enzyme activity in low substrate concentrations, completely reversed the liberation of K by acetyl choline at all concentrations of substrate used. These results are explainable on the basis of the enzyme possessing two active sites (one combining with the ester group, the other with the N group of acetyl choline) which have different affinities for active groups in the different inhibitors.

FATE OF BACTERIAL PYROGENS IN THE RABBIT. *Grace P. Kerby (introduced by E. A. Stead, Jr.)* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

The fate of pyrogens in the splanchnic circulation has been studied by a technic of combining a continuous intravenous infusion of pyrogen into the intact rabbit with the simultaneous withdrawal of blood samples by cardiac puncture and through a hepatic venous catheter. A slight decrease in pyrogenic activity of hepatic venous blood as compared to cardiac blood is noted in pyrogen-tolerant rabbits but not in

normal rabbits. There are no data in the present studies to demonstrate that this disappearance of pyrogen occurs only in the splanchnic area.

In vitro exposure of pyrogens to normal and to pyrogen-tolerant plasma at 5°C. and 37°C. resulted in a slight decrease in pyrogenic activity on exposure of pyrogen to pyrogen-tolerant plasma at 37°C. No other significant differences were noted. No evidence of alteration of pyrogen by the circulating blood cells was obtained.

These studies demonstrate the need for a method of pyrogen assay involving fewer variables than are encountered in the present method of following temperature response in individual recipient rabbits.

INFLUENCE OF pH UPON THE BLOOD FLOW AND PERIPHERAL RESISTANCE IN THE HIND LEG OF THE DOG. *Nancy C. Kester, A. W. Richardson (by invitation) and H. D. Green.* (From the Department of Physiology and Pharmacology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.)

In general little attention has been paid to the pH of solutions tested for vasomotor effects. Having observed that intra-arterial injections of sodium pentobarbital, which has a very high pH, resulted in marked vasodilatation, we decided to investigate whether the vasodilator effect could be due to the pH of the solution. We prepared a four-component buffer solution with a pH range of 2 to 11. One ml. quantities of this solution adjusted to various pH values were injected intra-arterially while recording flow in the hind leg of a dog with an electromagnetic flowmeter. A minimum change in flow was observed with solutions of pH 7.4 (115 per cent of control) but as the pH was changed in either direction flow increased so that at pH 2.0 it was 217 per cent of control and at pH 10.0 it was 234 per cent of control. The estimated change in blood pH produced by the injection at pH 2.0 was −0.87 and by the injection at pH 10.0 was +0.70. Larger changes in blood pH were required on the acid than on the alkaline side to produce comparable increases in flow. The results suggest that a physiologic mechanism exists which is designed to restore homeostasis of [H+] or [OH−] concentration with disturbance on either side of physiologic range.

EFFECTS IN MAN OF THE HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR OF THE PANCREAS. *Robert F. Kibler, W. Jape Taylor (by invitation) and J. D. Myers.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

Studies in animals have indicated that the hyperglycemic-glycogenolytic factor (HGF) of the pancreas is potent in increasing blood sugar by promoting hepatic glycogenolysis. The technic of hepatic venous catheterization has been utilized to study the effects of HGF in (1) hospital patients without significant hepatic or other disease and (2) patients with various disorders which would be expected to affect hepatic glycogen content.

In six fasting persons without significant disease, HGF 5 mg. intravenously, caused a mean rise in arterial blood glucose of 22 mg. per cent within ten minutes. Hepatic venous glucose concentration rose more abruptly and more intensely to a mean of +36 mg. per cent within five minutes. Splanchnic glucose production increased at the peak to 250 per cent of the control value. These results in the control group of subjects were very consistent.

Preliminary studies in Laennec's cirrhosis, hyperthyroidism, and states of malnutrition, conditions in which hepatic glycogen would be expected to be reduced, have shown a subnormal response to HGF as judged by augmentation of arterial blood glucose concentration. Two patients with myxedema have given normal responses.

It may be concluded that HGF causes hyperglycemia in man by strikingly increasing splanchnic, presumably hepatic, glucose production. The response to the material may prove to be a measure of hepatic glycogen content.

STUDIES ON THE EFFECTS OF MODIFIED HUMAN GLOBIN. *L. H. Kyle, W. C. Hess and W. P. Walsh (introduced by Harold Jeghers).* (From the Departments of Medicine and Biological Chemistry, Georgetown University School of Medicine and the Georgetown University Hospital, Washington, D. C.)

Modified human globin,® prepared from human red blood cells, has been administered thirty-two times to twenty-eight patients, a total of 295 separate infusions. In most instances 2 units (32 gm.) were given daily for five successive days. Intravenous administration of this protein preparation in sodium chloride, glucose or distilled water was associated with a low incidence of mild toxic reactions, such being related to both individual lots and the rapidity

of infusion. It disappeared rapidly from the blood and only minimal amounts were excreted in the urine. That globin does not migrate with facility into loculated fluid compartments is demonstrated by the small amounts present in pleural or peritoneal transudate. Globin therapy produced a positive nitrogen balance and in hypoproteinemic patients there was a significant increase in plasma proteins. The degree of blood protein elevation, in relation to the amounts of globin infused, as well as the rapidity of such elevation suggests that globin may be converted directly into plasma protein. A significant elevation of serum albumin, measured both chemically and electrophoretically, was effected only in those patients with low serum albumin levels.

In two of four patients with nephrosis the administration of globin was accompanied by a rapid loss of edema. One cirrhotic patient with edema and ascites showed no response to two separate courses of globin and, unlike all other hypoalbuminemic patients, failed to demonstrate a rise in serum albumin.

It appears from these observations that modified human globin is a safe and useful source of protein, preferable in many respects to plasma or protein hydrolysates, with an especially marked effect on blood protein.

CORRELATION OF THE VITAMIN A TOLERANCE CURVE WITH THE DEGREE OF FAT ABSORPTION. *Clarence W. Legerton, Jr., E. Clinton Texter, Jr. and J. M. Ruffin (introduced by J. D. Myers).* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

The five-hour vitamin A tolerance test was compared with the per cent of fat absorption as measured by the five-day fecal fat balance study to ascertain if a consistant correlation was present, in the hope that the simpler determination of vitamin A might replace the laborious balance studies in measuring the degree of steatorrhea. Fecal fat was determined by means of the wet extraction technic. Vitamin A was administered in the form of oleum percomorphum,® 0.1 cc. per pound of body weight orally, with blood vitamin A levels determined at three and five hours.

Thirty-three tests were performed on a total of twenty-seven patients. Nineteen of these had steatorrhea, while four healthy males and four patients without gastrointestinal disease were studied as a control group. These cases were divided into six groups based on the amount of fat absorbed as measured by the fat balance test (above 95 per cent, 90–95, 85–90, 80–85, 75–80 and below 75 per cent).

The vitamin A blood levels rose rapidly in the eight cases having fat absorption in excess of 95 per cent. The minimum vitamin A level at five hours was 366, the maximum 688, and the mean 489 gamma per cent. In eight cases having less than 75 per cent fat absorption the vitamin A blood levels remained flat. The maximum five-hour level was 68, the minimum 6 and the mean 38.5. In the remaining seventeen tests (75 to 95 per cent fat absorption) there was a direct correlation between the vitamin A tolerance curve and the percentage of fat absorbed.

The absorption of vitamin A from an oily vehicle parallels the degree of fat absorption as measured by fecal fat balance studies.

NOR-EPINEPHRINE—THE EFFECT ON RENAL HEMODYNAMICS. *Lewis C. Mills, James Skelton (by invitation) and John H. Moyer.* (From the Departments of Medicine and Pharmacology, Baylor University College of Medicine and the Cardiac Clinic, Jefferson Davis Hospital, Houston, Tex.)

The effect of nor-epinephrine on renal hemodynamics was studied because of its potential therapeutic value as a vasopressor agent and because of its value as an investigative tool. The effect on glomerular filtration rate and renal plasma flow was determined in nine normal patients, and on glomerular filtration rate and TmPAH in another nine. In addition, effects on blood pressure, hematocrit, blood sugar and sodium and potassium excretion were evaluated.

Following the constant intravenous administration of from 0.182 to 0.809 μg./kg./min., the mean blood pressure increased about 30 per cent; the renal plasma flow decreased 40 per cent due to a marked increase in renal vascular resistance. The glomerular filtration rate decreased only 8 per cent. There was no significant alteration of TmPAH, indicating constancy of tubular activity. Tubular transport of sodium and potassium was altered. The urine volume, hematocrit and blood sugar were increased.

These observations were interpreted as indicating that nor-epinephrine is a renal vasoconstrictor and that the predominant effect is on the efferent arterioles. The decrease in renal plasma flow in the absence of a change in TmPAH indicates a decrease in circulation to each individual nephron rather than shunting mechanisms or changing numbers of functioning nephrons.

CEREBRAL HEMODYNAMIC EFFECTS OF AMINOPHYLLINE IN THE TREATMENT OF PATIENTS WITH HYPERTENSIVE HEADACHES. *John H. Moyer and (by invitation) Sam I. Miller, Arthur B. Tashnek and Harvey Snyder.* (From the Departments of Medicine and Pharmacology, Baylor University College of Medicine and the Jefferson Davis Hospital, Houston, Tex.)

During the course of evaluating the cerebral effect of intravenous aminophylline® it was noted that this drug gave prompt and complete relief of headaches associated with severe hypertension. For this reason a study on the effect of aminophylline (0.5 gm. intravenously) on cerebrovascular hemodynamics, cerebrospinal fluid pressure and cerebral metabolism was undertaken in nine patients exhibiting hypertensive headaches. Similar studies were conducted in seven patients to whom caffeine (0.5 gm.) was administered instead of aminophylline.

Aminophylline caused a significant increase in cerebrovascular resistance and a decrease in cerebral blood flow (mean of 53 for the group reduced to 36 cc./100 gm./minute). Headache was relieved in all those patients in whom the cerebral blood flow decreased. This was also associated with a sharp reduction in cerebrospinal fluid pressure (mean of 210 reduced to 132 mm. water). The mean (group) jugular venous pressure decreased 13 mm. water. Cerebral metabolism as noted in oxygen and glucose uptake was not altered. Caffeine showed similar effects on cerebral dynamics but they were less dramatic and less consistent. These observations were interpreted to indicate that the cerebrospinal fluid pressure is decreased due to a reduction in arterial blood flow into the head, thus reducing the intravascular volume. The relief of headaches is probably due to reduced capillary and perivascular tissue pressure surrounding and distal to the constricted arterioles.

HOMOGENOUS RENAL TRANSPLANTS AFTER BILATERAL NEPHRECTOMY. *E. E. Muirhead.* (From the Department of Pathology, Southwestern Medical School of the University of Texas, Dallas, Tex.)

Dogs have been maintained by means of peritoneal irrigation after removal of both kidneys for intervals of approximately twelve or fourteen days. At this time a homogenous kidney was transplanted to the neck of the bilaterally nephrectomized animal and its activity appraised.

Following bilateral nephrectomy and the use of peritoneal irrigation, hypertension and a moderate azotemia developed. The implantation of the homogenous kidney was followed by profuse diuresis, a recession of the azotemia to normal level and a precipitous drop in the blood pressure. These changes continued for several days and were followed subsequently by a reappearance of the hypertension and of the azotemia. The specific gravity of the urine from this kidney was increased during the first week but subsequently remained fixed and low. The urine urea concentration dropped from a normal level to a markedly low level. Beginning at approximately ten days, renal function deteriorated until eventually oliguria and anuria appeared during the third or fourth week.

Homogenous kidneys have been more effective than peritoneal irrigation for the clearance of nitrogenous waste products up to ten days time. Homogenous kidneys have also affected a recession in the hypertension occurring after bilateral nephrectomy.

INTER-RELATIONSHIP BETWEEN SPLANCHNIC BLOOD FLOW AND SPLANCHNIC METABOLISM. *J. D. Myers and (by invitation) W. Jape Taylor.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

Considerable experience has been accumulated with splanchnic (hepatic) blood flow (HBF) and splanchnic oxygen consumption (sp O_2) under various physiologic and pathologic conditions. The normal sp O_2, 58 ml. per minute, is maintained by an HBF of 1,330 ml. per minute and an hepatic A-V oxygen difference (A-V O_2) of 4.4 volumes per cent. These conditions are retained by most persons with Laennec's cirrhosis, arterial hypertension, diabetes mellitus and erythremia.

It is difficult to increase HBF without increasing sp O_2. This may at times be accomplished in sudden and large expansion of the plasma volume. In general, HBF is not increased unless sp O_2 is elevated (epinephrine, fever) or unless severe anemia is present. Other conditions which elevate sp O_2 (hyperthyroidism, chronic leukemia with hepatosplenomegaly, and the intravenous administration of amino acids) do so by increased oxygen extraction (high A-V O_2) without augmenting HBF. These conditions are therefore associated with considerable degrees of unsaturation of hepatic venous blood. Where HBF is significantly reduced (low-output heart failure, some instances of Laennec's cirrhosis, acute hepatitis and obstructive jaundice, as well

as with exercise and orthostasis—Bradley), sp O_2 is usually well maintained by increased oxygen extraction, and again hypoxemia results. Only when total sp O_2 is reduced (myxedema, and certain instances of atrophic Laennec's cirrhosis) is HBF subnormal without increased oxygen extraction.

PATTERNS OF ARTERIAL PRESSURE RESPONSE TO SUDDEN CHANGE IN BODY POSITION. *John L. Patterson, Jr. and (by invitation) Paul W. Seavey.* (From the Departments of Medicine and Physiology, Emory University School of Medicine, Atlanta, Ga.)

Continuous recording of arterial pressure with tilting has disclosed phenomena not previously described in man.

Arterial pressure and respiration were recorded with strain gauges and Sanborn Polyviso in twenty-three subjects before, during and after 65° head-up tilting. With rare exception, the fluctuations in pressure with each respiratory cycle were increased several fold in the upright position, to a maximum of 40 mm. Hg. In one-half the subjects a distinctly different type of oscillation appeared, either spontaneously or following speaking, more often after nitroglycerine administration. This consisted of waves of large 20 to 50 mm. Hg amplitude and 4 per minute frequency. In two subjects, intravenous atropine abolished variations in heart rate but not the pressure oscillations. In three subjects with vasodepressor syncope and two with syncope from postural hypotension the mean arterial pressure at the faint averaged 9 mm. Hg at head level and the pulse pressure 10 mm. Hg.

Rhythmic vasomotor activity or variations in cardiac filling must be postulated to explain these pressure phenomena. The slow-frequency oscillations bear certain resemblances to the Traube-Hering waves in experimental animals. The extremely small pulse pressures and bradycardia at the faint indicate that the stroke volume and cardiac output must also be very small at this time.

PHARMACODYNAMIC STUDIES ON REGITINE, A NEW ADRENERGIC BLOCKING DRUG (CIBA 7337): 2-N-p′-tolyl-N-(m′-hydroxyphenyl)-aminomethyl hydrochloride. *Gwen Roberts, A. W. Richardson (by invitation) and H. D. Green.* (From the Department of Physiology and Pharmacology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.)

Femoral arterial blood flow, measured by the electromagnetic flowmeter of Richardson, Denison and Green, and arterial pressure taken just distal to the flowmeter by a Statham pressure gauge were shown to be appreciably modified by small amounts of intra-arterial regitine.® Doses of 0.15, 0.1 and 0.015 mg./kg. resulted in very variable decreases in peripheral resistance, post-injection flows ranging from 420 to 85 per cent of control flow. The magnitude of response had no apparent correlation with the amount of regitine injected, size of the animal, control blood flow or arterial pressure, type of control response to epinephrine, or with other factors such as the time since the last injection of anesthesia. Tachyphylaxis rapidly developed as indicated by the rapid decrease in vasodilator response to successive injections of regitine in the same animal. Intra-arterial injection of 0.15 mg./kg. caused the vasoconstrictor response to 1 μg. of epinephrine intra-arterially (180 per cent of control peripheral resistance) to be converted to vasodilation (70 per cent of control peripheral resistance). Reversal was maximum within fifteen minutes and subsequent injections of epinephrine showed a gradual return to control response of epinephrine in four to eight hours. After 0.1 mg./kg. the reversal could be elicited for a shorter time.

EFFECT OF TRIETHYLENE MELAMINE ON SERUM PROTEIN COMPONENTS IN PATIENTS WITH MALIGNANT DISEASE. *R. W. Rundles and (by invitation) Tulio Arends.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

The administration of TEM produces severe cytotoxic effects in lymphoid tissues and in bone marrow. Since some globulin constituents of the serum are thought to be produced by the hemopoietic tissues, normally as well as in disease states, changes in serum protein composition were studied during prolonged TEM therapy.

A patient with active Hodgkin's disease developed a severe hemolytic anemia, with a positive direct Coombs' test, and auto- and isoagglutination in high dilution, unchanged by splenectomy. After TEM therapy hemolysis ceased and the abnormal antibody disappeared.

The sera of fourteen patients with hemopoietic and other malignancies were studied by electrophoresis before and after therapy. Four of ten patients with lymphocytic leukemia or lymphoma had abnormal globulin components, one of them with cryoglobulinemia and one had no gamma globulin. After TEM therapy the ab-

normal components were significantly reduced. A gamma component in the serum of one of the two patients with multiple myeloma fell from 38 to 31 per cent with the administration of TEM. Full therapeutic doses of TEM over a period of weeks or months had little or no effect on normal serum protein constituents.

EFFECTS OF AGE ON CEREBRAL BLOOD FLOW AND METABOLISM. *P. Scheinberg and (by invitation) H. W. Jayne, I. Blackburn and M. Rich.* (From the Department of Experimental Medicine, University of Miami Medical Research Unit, and the Department of Medicine, Veterans Administration Hospital, Coral Gables, Fla.)

Studies of cerebral circulation and metabolism in various disease states involving middle-aged or elderly persons cannot be adequately interpreted unless the effects of the ageing process itself on these functions are known. In this study cerebral blood flow and metabolism were measured by a modification of the nitrous oxide technic in thirty-five normal male subjects, varying in age from thirty-eight to eighty-two years.

As compared to a group of thirty-two normal young males (ages eighteen to thirty-six), the following changes were noted: cerebral blood flow, 15 per cent reduction; arterial-cerebral venous oxygen difference, 9 per cent increase; cerebral oxygen consumption, no change; cerebral vascular resistance, 40 per cent increase. Separate consideration of the nineteen subjects above the age of fifty-five revealed a tendency for a reduced cerebral oxygen consumption, which further studies may reveal to be significant. There is an excellent statistical correlation ($p < 0.01$) between age and cerebral blood flow and between age and cerebral vascular resistance, blood flow decreasing and vascular resistance increasing with advancing age. That the increased vascular tone is not necessarily fixed is demonstrated by a presumptive increase in cerebral blood flow of 200 to 300 per cent following inhalation of 10 per cent CO_2 to 90 per cent O_2 mixture.

CONTROL OF HYPERTENSION WITH HEXAMETHONIUM AND HYDRAZINOPHTHALAZINE. *Henry A. Schroeder.* (From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Mo.)

Sixty patients suffering from hypertension of all degrees of severity have been given l-hydrazinophthalazine in oral doses up to 900 mg. per day and hexamethonium chloride in doses up to 6.0 gm. per day. In malignant hypertension supplementary initial doses of hexamethonium bromide were given parenterally. One drug was first administered for several days and the other added. The elevated blood pressure in benign hypertension was controlled at normotensive or near normotensive levels in almost every case. The malignant stage reversed itself in eighteen of twenty cases, but in only five were strictly normotensive levels sustained, and three reverted to the malignant stage when the drugs were discontinued. Tolerance developed in two of the most severe cases of malignant hypertension. The longest period of observation was four months. At home patients were taught to control their own levels of blood pressure by varying the doses of hexamethonium. l-Hydrazinophthalazine inhibits the pressor action of pherentasin and of hypertensin; hexamethonium produces autonomic block. The two drugs provide a practical if somewhat cumbersome way of controlling elevated arterial pressure for periods as long as four months. Great care in administration is necessary in order to prevent accidents due to hypotension.

SOME MECHANISMS OF ALKALOSIS INDUCED BY ACTH ADMINISTRATION. *D. S. Seldin and M. Walser (by invitation) and C. H. Burnett.* (From the Department of Internal Medicine, Southwestern Medical School of the University of Texas, Dallas, Tex.)

A metabolic balance study of the hypochloremic, hypokalemic alkalosis arising during ACTH administration was undertaken. With the patient on a constant diet, 250 mg. of ACTH were injected daily. Increased urinary losses of potassium, titratable acid and ammonia ensued, and profound hypokalemia and metabolic alkalosis developed. When sodium chloride was restricted from the diet these effects did not occur.

The ingestion of potassium phosphate (pH 6.8 and 7.5) and potassium sulfate corrected neither hypokalemia nor alkalosis, and failed to suppress ammonia or acid excretion. In contrast, potassium chloride produced an alkaline urine, suppressed acid and ammonia excretion, and quickly corrected hypokalemia and alkalosis. Ammonium chloride accelerated the excretion of potassium, ammonia and acid, failing to correct the alkalosis and aggravating hypokalemia.

It is suggested that when dietary salt is given, adrenal steroids, by accelerating renal tubular reabsorption of sodium, enhance potassium ex-

cretion, probably by ion exchange. While potassium deficiency develops, greater amounts of titratable acid and ammonia are excreted. The severe alkalosis which develops is refractory to ammonium chloride because, as long as potassium deficit remains, administered acid is promptly excreted. KCl, by repairing the potassium deficit, represses acid excretion and ammonia production, and is the ideal repair substance.

PRIMARY THROMBOSIS OF THE INTERNAL CAROTID ARTERY: STUDIES OF THE CEREBRAL CIRCULATION IN THREE CASES. *Willis Sensenbach and Leonard Madison (introduced by E. E. Muirhead).* (From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, Southwestern Medical College of the University of Texas, Dallas, Tex.)

The diagnosis of primary thrombosis of the internal carotid artery was established in three cases by cerebral angiograms, surgical exploration or both. The nitrous oxide method for the determination of cerebral blood flow was employed in studies of the cerebral circulation in these patients. The results indicate that complete interruption of the flow of blood through one internal carotid artery does not lead to significant impairment of blood flow to the brain unless there are associated cerebral vascular defects such as generalized cerebral arteriosclerosis or a deficient anastomotic pathway at the circle of Willis, or both.

In one of the patients an attempt was made to increase the supply of arterial blood to the brain by the construction of a common carotid artery-internal jugular vein fistula on the side of the thrombosed internal carotid artery. This procedure was ineffective in this patient.

EFFECTS OF ACTH AND CORTISONE ON CEREBRAL CIRCULATION AND METABOLISM. *Willis Sensenbach and Leonard Madison (introduced by E. E. Muirhead).* (From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, Southwestern Medical College of the University of Texas, Dallas, Tex.)

Studies of the cerebral circulation and cerebral metabolism were made during the administration of cortisone and ACTH. Cerebral blood flow (CBF) was determined by the nitrous oxide method, mean arterial blood pressure (MABP) measured directly, and cerebral vascular resistance (CVR), cerebral oxygen (CMR O_2) and glucose (CMRglu) consumption calculated in the usual manner. These functions were determined before, one or more times during, and again after the administration of ACTH and cortisone in doses of from 80 to 120 mg. daily.

Seventeen determinations were made on eleven patients during the administration of ACTH, nine determinations on seven patients receiving cortisone. The mean CBF in both the ACTH and cortisone-treated patients was unchanged as compared with the pretreatment control values. Slight increases in mean CVR and mean CMR O_2 occurred in both ACTH and cortisone-treated groups but the changes were not of statistical significance. The only significant change observed was an increase in MABP in those patients treated with ACTH. Personality changes varying from mild euphoria to frank psychoses were common. No correlation between changes in personality and cerebral blood flow or metabolism could be made.

RESPONSE OF NORMAL AND DISEASED RETINAL VESSELS TO CHANGES IN BLOOD OXYGEN TENSION. *Herbert O. Sieker (by invitation) and John B. Hickam.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

During life vascular disease is evident mostly through secondary effects of ischemia. These are late effects. There is need for more direct means of finding and following degenerative vascular disease. It is known that normal retinal arteries and veins will constrict when the blood oxygen tension is increased and dilate when it is lowered. The present study was undertaken to determine whether this reaction is altered in persons with known vascular disease.

Eyeground photographs were taken with a fundus camera while the subjects breathed air, tank oxygen and, in some cases 5 per cent CO_2 or 10 per cent O_2. The diameter of the larger vessels was measured with a low-power microscope having a scale engraved on the ocular. Measurements were made on normal subjects and patients with hypertension and with diabetes.

The arteries of hypertensive and diabetic patients and the veins of the diabetics showed significantly less reactivity than normal vessels. Many of the diabetic patients also had hypertension, but the diabetics as a group had significantly less ($p < 0.05$) arterial reactivity than the hypertensives.

The cause of this altered reactivity is not yet established, but its relation to vascular disease and the simplicity of the technic indicate that it deserves further study.

OBSERVATIONS ON THE HEPATIC CIRCULATION IN ACUTE HEPATITIS AND IN OBSTRUCTIVE JAUNDICE. *W. Jape Taylor (by invitation) and J. D. Myers.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

Ten subjects in various stages of infectious hepatitis and seven patients with obstructive jaundice have been studied by hepatic venous catheterization. Nine of the ten cases of hepatitis showed an oxygen difference between arterial and hepatic venous bloods which was greater than normal. The mean hepatic A-V oxygen difference for all ten cases of hepatitis, 5.5 volumes per cent, is statistically greater than the control mean of 4.3 ($p < 0.01$). Likewise in five of the seven instances of obstructive jaundice the hepatic A-V oxygen difference was high, and again the mean for seven cases, 5.4 volumes per cent, is significantly greater than the control ($p < 0.01$).

A high hepatic A-V oxygen difference in general indicates either a decreased hepatic blood flow or an increase in splanchnic oxygen metabolism. Hepatic blood flow cannot be accurately measured in jaundiced persons by present technics but our studies, although admittedly inaccurate, indicate a subnormal rate of hepatic blood flow. This in turn could be related either to a reduced total circulation, to splanchnic vasoconstriction or to intrahepatic obstruction. Against the first possibility is the demonstration in about half of the above patients of an essentially normal arterial-right atrial oxygen difference. It is suggested that in both acute hepatitis and severe obstructive jaundice there is intrahepatic obstruction to blood flow.

DISAPPEARANCE OF RADIOACTIVE TAGGED ALBUMIN FROM THE SERUM AND EXCRETION OF I^{131} IN THE URINE OF PATIENTS WITH CIRRHOSIS. *Malcolm P. Tyor (by invitation), Jerry K. Aikawa and David Cayer.* (From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.)

The rate of disappearance of tracer amounts of iodinated albumin tagged with I^{131} from the blood and the rate of excretion of urinary radioiodide have been determined in nine patients with cirrhosis of the liver and twenty-two persons with various other disease states. The mean values for the relative concentrations of iodinated albumin in the serum at 3, 6, 12 and 24 hours after injection were similar in the two groups. A statistically significant decrease in the urinary excretion of inorganic iodide was found during the first twenty-four hours in the patients with cirrhosis as compared with other diseases.

Three possible explanations for the reduced rate of urinary excretion of inorganic iodide in the cirrhotic group are: (1) impaired renal excretion, but accumulation in the serum was not detected; (2) increased uptake by the thyroid gland, but the amount of radioactivity injected was too small to detect by standard external counting technic; and (3) a slower rate of albumin catabolism. From these and other data accumulated the last hypothesis seems the most likely.

CORTISONE AS ADJUNCT TO CHLORAMPHENICOL IN THE TREATMENT OF ROCKY MOUNTAIN SPOTTED FEVER. *J. B. Workman, H. A. Hightower, F. Borges, E. Furman and R. T. Parker (introduced by Theodore E. Woodward).* (From the Section of Infectious Diseases, Department of Medicine, School of Medicine, University of Maryland, Baltimore, Md.)

Results of combined chloramphenicol-cortisone therapy in nine cases of Rocky Mountain spotted fever, three of which were classified as late cases, are presented. Diagnosis was based upon the typical history and physical findings of the disease and demonstration of a rising or significantly elevated titer for Proteus agglutinins and specific complement fixing antibodies. Therapy consisted of oral chloramphenicol (chloromycetin®) in doses of approximately 50 mg./kg./day and was continued until patients had been afebrile for forty-eight hours. Cortisone (cortone®) was administered orally or intramuscularly in an initial dose of 200 mg. followed by two 100 mg. doses at six-hour intervals. Children received approximately two-thirds the adult dose. In no instance did the total dose of cortisone exceed 400 mg. or did the period of administration exceed twelve hours. No untoward side effects from cortisone therapy were noted.

On an average, therapy was begun on the sixth day of disease and the mean duration of fever after institution of combined therapy was 1.7 days. The striking effect of combined therapy was manifest by rapid alleviation of headache and toxicity with a return of appetite and sense of well being within a twenty-four-hour period.

Routine use of cortisone is not indicated in the treatment of Rocky Mountain spotted fever. The combination of antibiotic and excellent supportive therapy is mandatory in the treat-

ment of patients first observed late in the course of disease. The results of cortisone in this limited series of patients warrant further clinical testing.

ENDOCRINE ACTIVITIES IN THE CONTROL OF RENAL TUBULAR CONCENTRABILITY. *James T. Wortham (by invitation) and Benjamin B. Wells.* (From the Department of Medicine, University of Arkansas School of Medicine, Little Rock, Ark.)

In performing urine concentration tests with pitressin® variability in the results was discovered in normal subjects. Standardization of test conditions yielded results as follows:

Normal females were given pitressin tests under several controlled conditions. While at rest the subjects concentrated to 1.026 or above consistently whether they had been previously fasted or not. Moderate, forced exercise during the test abolished the pitressin effect on urine concentration. Likewise, small amounts of water given before the test resulted in significant abolition of the pitressin effect. Since pitressin is physiologically identical with the antidiuretic hormone of the posterior pituitary (ADH), it seems evident that water diuresis is significant in opposing ADH effect but that some factor inherent in physical activity is more potent in opposing ADH effect.

Adrenal cortical steroids are under study for this anti-ADH effect. Moderate doses of desoxycorticosterone acetate were given two hours before a pitressin test. It was found that the pitressin effect was abolished. The pitressin test was performed, theoretically, while renal tubules were under the influence of DOCA but before any significant shift in fluid compartments could have occurred.

Other steroids under study promise to reveal significant effects. An attempt is being made to determine whether exercise opposes the ADH effect through adrenal cortical activation.

COMPARISON OF THE ACTION OF VARYING CONCENTRATIONS OF EIGHT ANTIBIOTICS AGAINST PSEUDOMONAS AERUGINOSA. *Ellard M. Yow.* (From the Department of Internal Medicine, Baylor University College of Medicine, Houston, Tex.)

The resistance of most strains of Pseudomonas aeruginosa to the action of the commonly used antimicrobial agents has increased its relative importance and frequency as a causative agent in infectious processes. This study was undertaken in an effort to determine the most effective therapy against infections due to this microorganism.

Fifty-four strains of pseudomonas recently isolated from patients were tested for sensitivity by the tube dilution technic to varying concentrations of penicillin, streptomycin, bacitracin, neomycin, aureomycin, chloramphenicol, terramycin and polymyxin B. At an antibiotic concentration of 15.6 μg./ml., all of the strains tested were sensitive to polymyxin B, 57 per cent were sensitive to neomycin, 55 per cent to terramycin, 42 per cent to streptomycin, 8 per cent to aureomycin, 2 per cent to chloramphenicol and none of the strains was sensitive to penicillin or bacitracin. At a level of 1.0 μg./ml., 62 per cent of the strains tested were sensitive to polymyxin B, 6 per cent to streptomycin, but none were sensitive to the other antibiotics studied. A comparison of the sensitivity at other levels was made and the significance of such determinations on the clinical administration of these antibiotics is discussed.

A similar study was performed using the disk sensitivity technic against 100 strains of pseudomonas. A comparison of the results obtained by the two methods revealed a relatively close qualitative but not quantitative correlation.

Thirty-eight patients with pseudomonas infections were treated. Polymyxin B was the most consistently effective antibiotic clinically although terramycin favorably influenced the course of the infection when the causative organism was sufficiently sensitive.

Case Report

American Mucocutaneous Leishmaniasis Successfully Treated with 2-Hydroxystilbamidine*

I. SNAPPER, M.D.
New York, New York

THE favorable influence of the diamidines, stilbamidine and pentamidine, on kala-azar is well known. Unfortunately, the use of stilbamidine, the more potent of these two preparations, is associated with grave toxic side actions. However, another diamidine derivative, 2-hydroxystilbamidine, which is known to be leishmanicidal *in vitro*, and also inhibits the growth of bacteria and fungi, has proved to be much less toxic for humans. It is the purpose of this report to recount in some detail the successful treatment with 2-hydroxystilbamidine of the visceral manifestations of American mucocutaneous leishmaniasis, a condition which has received scant attention.

CASE REPORT

A twenty-three year old white female writer was admitted to the Mount Sinai Hospital because of an infection of the chest wall and multiple ulcerations of the skin and mucous membranes. The patient's home is in Oklahoma but over the four years prior to admission she had travelled extensively in the tropics. She lived in Mexico during 1947 and 1948 and travelled in 1949 for six months through the subtropical jungle of the Santiago-Zamora region of Ecuador. There she was well except for transient cystitis, diarrhea and avitaminosis. She spent October, 1949, through March, 1950, in Piendamo, Colombia, where she experienced several episodes of chills, fever and "biliary colic" recurring every other day, aborted by paludrine and liver extract. The following year she returned to Oklahoma and was well. The present illness began in the first week after her return to Colombia in February, 1951, when, in Medellin, she noted fever, pharyngitis and laryngitis. In the week following, chills and "biliary colic" were controlled with paludrine and liver extract. In the third week the patient had symptoms of "influenza" with complete recovery. But in March, 1951, the fifth week after her arrival in Colombia, she had sudden onset of chills, weakness and tender mouth swelling which were regarded as Plaut-Vincent's angina. The mouth lesions improved on a regimen of quinine, penicillin, vitamin B complex and liver extract, but fever persisted and new lesions resembling "boils" developed on the forehead and within the nose, with marked surrounding edema and swelling. Considerable enlargement of tender preauricular and submandibular lymph nodes required incision with drainage of a preauricular node. Despite three weeks of treatment with chloromycetin and aralen fever persisted unabated, reaching 104°F., and jaundice and marked rectal pain were noted. Supportive therapy was given, including whole blood transfusions, glucose infusions, folic acid, vitamin B and a high caloric, high protein diet. Despite a protracted course of terramycin fever persisted, ranging daily to 102 to 103°F. and falling at night. Codeine was administered for a persistent cough. In the fourth week of illness a rectal boil was incised, followed by persistent drainage, and new boils on the right arm and near the ear were incised repeatedly. The patient's general condition deteriorated rapidly and her weight fell from 135 to 85 pounds. A course of aureomycin in dosage of 4.5 gm. daily was now instituted but fever continued unchanged. In the second month of illness the patient began to complain of intense deep pain in the region of the left clavicle where a swelling appeared. On several occasions areas of softening were incised but only

* From the Second Medical Service of the Mount Sinai Hospital, New York, N. Y.

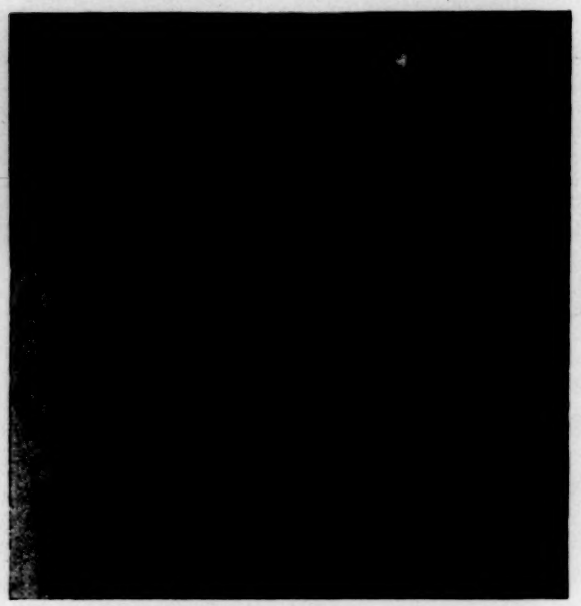

FIG. 1. Patient on admission to the hospital; large necrotic area with gangrenous crust.

thin serous fluid was obtained and at no time was purulent material found. The swelling increased in size and the pain became excruciating, despite liberal use of morphine derivatives and barbiturates. There was loss of use of the left arm. The skin overlying the clavicular swelling gradually blackened and became gangrenous, and the patient's temperature spiked above 105°F. Hemorrhages appeared on the skin of both arms and legs. The swelling of the chest wall now extended from the medial aspect of the left clavicle to the shoulders, and from the left breast to the back of the neck. Swallowing became difficult and painful. Finally, since the condition was considered hopeless, radiotherapy was instituted. After five treatments the pain and swelling were somewhat diminished and this slight improvement permitted the swallowing of liquids and soft foods. The heavy black necrotic crust which during radiotherapy had formed on the gangrenous area of the chest wall then separated, revealing deep and extensive underlying necrosis. Treatment at this time included streptomycin, intravenous penicillin, vitamin K, riboflavin and liver extract. With fever ranging to 102°F. and persistent vomiting of bile, the patient was flown to Miami where for two days in succession she was given vitamin and liver injections and 1 L. of whole blood, before being flown to New York.

Examination on admission to the Mount Sinai Hospital, nearly four months after this febrile illness had begun, revealed the patient to be a thin, pale, emaciated, white woman of twenty-three, appearing chronically ill. Temperature was 99 to 101°F., pulse 96, respiration 20, blood pressure 90/70. Examination of the skin revealed a healed pigmented scar on the right forehead, a pigmented, scarred, desquamating lesion on the left upper arm of 6 by 6 cm., a pigmented scar on the right upper arm of 4 by 4 cm., a scar of an incision above the latter lesion and a scar of an incision in the right preauricular area. The outstanding lesion was an irregular ulceration of the left upper anterior chest measuring 20 by 15 cm., and reaching from about 3 cm. above the clavicle to 10 cm. below the clavicle, covering practically the whole clavicle with the exception of the extreme lateral portion. A large, black, heaped-up, gangrenous crust 3 cm. high covered the ulceration. (Fig. 1.) The edges of the skin of the ulceration were pearly gray with a surrounding erythema.

At the time of admission no active lesions of the mucous membranes could be seen. A few days before departure from Colombia the last gangrenous masses had been expelled from the nose. The throat and tongue lesions had improved during the patient's stopover in Miami and on admission to the Mount Sinai Hospital solid food could be taken for the first time in ten days.

Small, firm, non-tender lymph nodes were palpable in both anterior and posterior cervical triangles, axillas, groins, femoral triangle and epitrochlear regions. The lungs were clear, the heart unremarkable and the neck without rigidity. A firm, smooth spleen was palpable two fingerbreadths below the costal margin. The lower pole of the right kidney was palpable. The liver was not felt. Rectal examination showed the presence of a fistula-in-ano. Remainder of physical examination was essentially negative.

Laboratory examination at the time of admission revealed a hemoglobin content of 11 gm. per cent, probably partly due to the many blood transfusions the patient had received in Colombia and the one received in Miami the day before admission. Extreme leukopenia was present with a total white count of only 850 per cm. (Table I.) The differential count revealed 19 per cent polynuclears (all staff forms), 60 per cent lymphocytes, 18 per cent monocytes, 2 per cent plasma cells and 1 per cent metamyelocytes. Platelets were 180,000 and reticulocytes 0.5 per

cent. The urine was normal with the exception of an occasional leukocyte. Serum albumin content was 3.4 gm. per cent, the globulin 4.2 gm. per cent. Bone marrow aspiration revealed an increase in myelocytes with a relative decrease in normoblasts and maturation arrest of segmented neutrophiles. (Table II.) No Leishman-Donovan bodies were seen. Culture of the ulceration of the chest wall revealed enterococci and Bacillus proteus. On repeated examination of the smears of the ulcer Leishman-Donovan bodies were finally found, mainly in the reticulum cells. Biopsy of the chest lesions revealed completely necrotic tissue covered by acute purulent exudate. In the biopsy no Leishman-Donovan bodies were found, probably due to the overwhelming secondary infection. The necrotic areas were surrounded by large masses of cocci and bacilli. Subcutaneous punctures were made under the margin of the ulceration and the material obtained was inoculated in N.N.N. media. All these cultures became contaminated and no flagellates grew out. X-ray examination of the left clavicle revealed a destructive lesion of the medial end of the clavicle. The bone had a moth-eaten appearance and there appeared to be a complete pathologic fracture at this site. Periosteal new bone formation was noted in the region of the lesion. The extent of the lesion was approximately 1 inch.

On admission the nature of the process was not immediately understood. The co-existence of granulocytopenia, fever, adenopathy and

TABLE I

AMERICAN LEISHMANIASIS TREATED WITH 2-HYDROXYSTILBAMIDINE (TOTAL 6.08 GM.)

Date	2-Hydroxy-stilbamidine Di-isethionate* (mg.)	Hemo-globin (gm.)	Total White Count	Polymorpho-nuclears (%)	Albumin/ Globulin	Platelets
1951 May 25	...	12	850	19	.....	180,000
May 27	...	....	1,100	12	.....	.....
May 28	...	....	1,200	20	.....	.....
May 30	225	....	.....	..	.....	.....
May 31	225	....	1,600	20	.....	.....
June 1	225	12	900	..	3.4/4.3	.....
June 2, 3, 4, 5	225	....	2,000	25	.....	200,000
June 6, 7	225	....	4,100	63	.....	200,000
June 9	225	....	5,950	64	.....	.....
June 11, 13	225	....	4,600	63	.....	.....
June 15	225	....	5,100	72	.....	.....
June 21	225	9.2	3,400	50	3.5/4.3	200,000
June 23–28	225	....	2,700	50	.....	115,000
June 29–July 7	225	11.8	4,900	36	.....	85,000
July 10	...	11.3	3,700	32	3.3/3.2	70,000
July 24	...	12.8	4,900	33	.....	130,000
July 31	...	13.0	5,600	30	.....	160,000
August 13	...	13.5	4,500	36	4.1/2.6	120,000
1952 March 3	...	14.3	6,600	54	4.1/2.6	130,000

* Twelve intravenous injections of 225 mg. of 2-hydroxystilbamidine between May 30th and July 15th and fifteen such injections between July 23rd and August 7th. Chloromycetin between June 7th and June 15th and between June 20th and July 9th.

TABLE II

STERNAL MARROW ASPIRATION

	5/25/51 (%)	7/19/51 (%)
Myeloblasts	1	3
Promyelocytes	...	4
Myelocytes	47	10
Metamyelocytes	...	12
Non-segmented polynuclears	24	16
Segmented polynuclears	...	4
Lymphocytes	2	9
Plasma cells	0.5	1
Reticulum cells	0.5	4
Erythroblasts	4	36
Normoblasts	19	..

splenomegaly in association with a destructive process of the left clavicle suggested that the process might represent a lymphoma, particularly reticulum cell sarcoma. This, however, was not corroborated by examination of the skin wound which revealed no evidence of lymphomatous infiltration.

Because of the patient's sojourn in the jungle areas of Ecuador, the presence of mucocutaneous lesions and fever without response to antibiotic therapy, a diagnosis of Brazilian mucocutaneous leishmaniasis was then made, which was later confirmed by the finding of Leishman-Donovan bodies in the smears of the ulcer over the clavicle. Since the condition of the patient was desperate, it was decided to treat her with a leishmanicidal drug.

Accordingly, on May 30th (five days after admission) intravenous injections of 225 mg. of 2-hydroxystilbamidine di-isethionate* dissolved in 200 cc. of 5 per cent glucose solution were given. These injections did not cause any discomfort. However, occasionally, when the drug was given dissolved in 10 cc. of water, a burning sensation in the gangrenous area was noticed.

One day after treatment was started the large necrotic mass fell off, revealing a dirty granulating area. Two days after the initiation of the 2-hydroxystilbamidine injections, on June 1st, the temperature, which had shown daily evening elevations to 101°F., became normal and remained normal until June 15th when the first course of injections totaling 2.7 gm. of 2-hydroxystilbamidine was terminated. The general condition improved rapidly so that on June 13th, two weeks after therapy was started, the patient became ambulatory. The white count progressively increased to values between 5,000 and 6,000. The number of granulocytes increased to nearly normal values and segmented polynuclears returned in the peripheral blood. Although thrombocytopenia with hemorrhagic tendency had been noted in Colombia, the platelet counts were now within normal limits. The hemoglobin fluctuated between 11 and 11.8 gm. per cent, the red blood cells between 4.43 and 4.48 million. During this period the chest wound progressively decreased in size, appeared cleaner and manifested evidence of granulation.

* From here on the term 2-hydroxystilbamidine will be used instead of 2-hydroxystilbamidine di-isethionate. The latter compound contains 53 per cent 2-hydroxystilbamidine.

On June 5th, during the hydroxystilbamidine treatment, vomiting and pains in the flanks developed. The urine contained a marked trace of protein and on microscopic examination showed the presence of 20 to 30 white blood cells per high power field. Several small clumps of white cells were seen. Urine culture revealed the presence of enterococci and proteus bacilli. The temperature remained flat. When on June 7th the pains persisted, chloromycetin was given and continued until June 16th. Since the patient had received large doses of chloromycetin in South America, it was considered highly improbable that this antibiotic could have had any influence on the leishmaniasis.

On June 15th, when the first series of diamidine treatment was terminated, the spleen was much smaller and was felt only 1 cm. below the costal margin. However, one week later, on June 22nd, the spleen was again enlarged and it was now felt three fingerbreadths below the costal margin. The leukocytes had decreased to 3,400 per cm., the hemoglobin to 9.2 gm. per cent and the serum globulin was still elevated to 4.3 gm. per cent. The temperature had risen again and patient was therefore started on a new series of injections of 225 mg. of 2-hydroxystilbamidine daily. These injections were continued until July 7th. During this second series another 3.4 gm. of the drug were given.

Just before initiation of the second course of 2-hydroxystilbamidine a petechial eruption had developed over both lower extremities. At the same time the platelets were somewhat lower than before, 140,000. During the second series of 2-hydroxystilbamidine injections the petechial eruption continued. The platelets went down to 115,000 on June 28th. On July 7th, when the second series of injections was terminated, the platelets were only 85,000. They remained low for a considerable time and even on August 13th, when the patient was in excellent condition, only 120,000 platelets were found.

Re-evaluation of the patient after termination of the second series of 2-hydroxystilbamidine injections showed that the general condition had improved considerably. In the six weeks since admission the patient had gained 20 pounds. The spleen was still felt two and a half fingerbreadths below the costal margin; it was blunt, firm and non-tender. The liver was now four fingerbreadths below the costal margin, blunt, irregular and tender. The surface of the liver was smooth, firm, and also somewhat

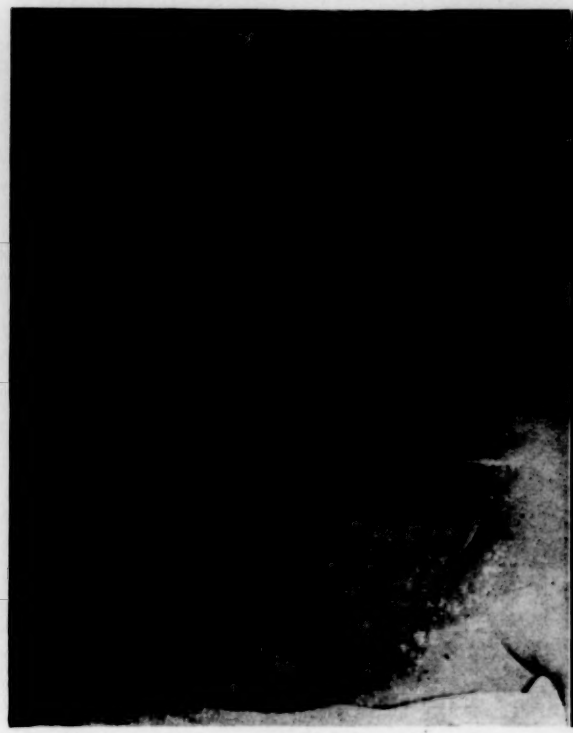

FIG. 2. Patient immediately after termination of 2-hydroxystilbamidine treatment; ulcerating area much reduced in size, clean and granulating; general condition improved.

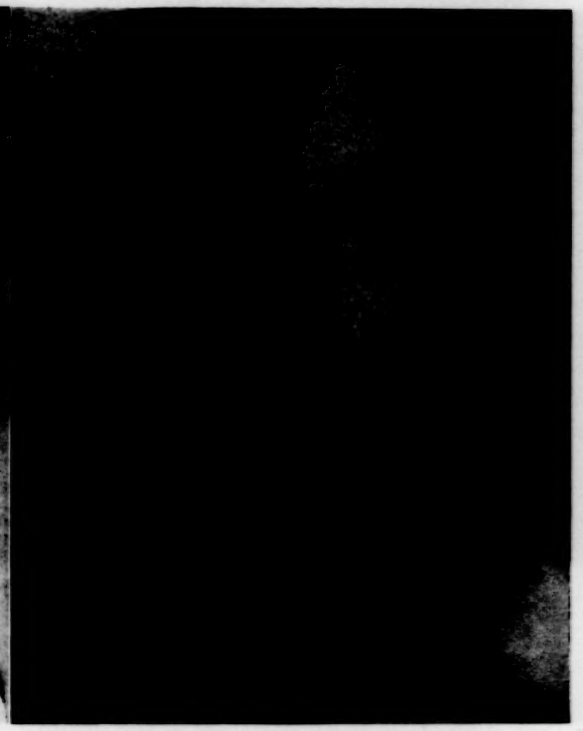

FIG. 3. Patient six weeks after termination of 2-hydroxystilbamidine treatment; necrotic area nearly completely epithelialized.

tender. The ulceration over the clavicle had decreased in size to an 8 by 6 cm. granulating area (Figs. 2 and 3) which at one point over the clavicular head communicated with the subjacent bone. There was alopecia of the scalp and lanugo of the face. Tenderness over the ulcer and over the lateral aspect of the clavicle was noted. The Rumpel-Leede test was negative. There were scattered petechiae on the buccal mucous membrane and hard palate. Several firm, non-tender, 0.5 to 1 cm. nodes were palpable in the posterior cervical and left supraclavicular region. A single left epitrochlear node, about 0.3 cm. in size, and shotty inguinal adenopathy were noted. Heart and lungs were unremarkable. The right kidney was ballotable. There was no evidence of ascites. A healed fistula-in-ano was noted.

The hemoglobin was 11.8 gm. per cent, red blood cells 5.09 million, white blood cells 3,700 with 26 per cent segmented, 6 per cent non-segmented, 46 per cent lymphocytes, 22 per cent monocytes. (Table I.) There were 80,000 platelets. Erythrocyte sedimentation rate was 22 mm./hr. Urine was normal except for occasional white blood cells. During a urine concentration test the specific gravity increased to 1.032. Phenolsulfonphthalein test was 60 per cent in one hour. B. proteus and Staphylococcus albus were obtained from the urine cultures. Culture of the chest wound also revealed B. proteus and Staph. aureus A. No fungi or molds were noted. Repeat marrow aspiration revealed slight increase in the erythroid elements. (Table II.) No Leishman-Donovan bodies were seen. Blood urea nitrogen was 14 mg. per cent, fasting blood sugar 105 mg. per cent. The serum total protein varied between 6.4 and 7.5 gm. per cent; serum albumin between 3.2 and 4.1 gm. per cent; serum globulin had come down to normal levels and was found to be 3.2 and later

TABLE III
SKIN TESTS

	After 24 Hours	After 48 Hours
Histoplasmin 1:100	Negative	Negative
Histoplasmin 1:1000	Negative	Negative
Coccidiomycin	2 mm. papule	Negative
Blastomycin	3 cc. erythema	Negative
Leishmania	2 mm. papule	2 mm. papule

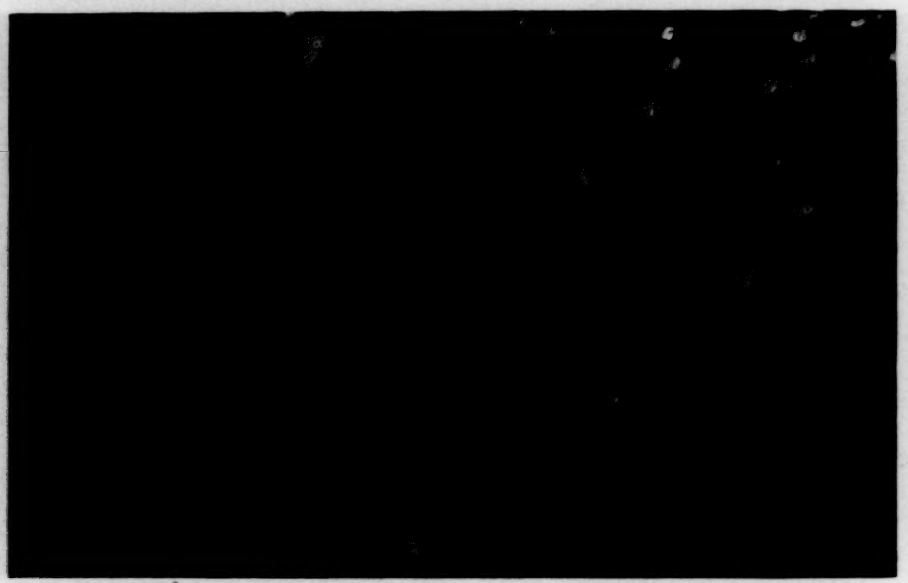

FIG. 4. Unstained microscopic section of liver biopsy, photographed with fluorescent microscope; nuclei of all liver cells strongly fluorescent due to presence of 2-hydroxystilbamidine.

2.5 gm. per cent. (Table I.) Bilirubin was 0.4 mg. per cent. The alkaline phosphatase of the serum was 12, 5 and 8 King-Armstrong units on three different occasions. The cephalin flocculation test was 4 plus shortly after termination of the 2-hydroxystilbamidine treatment and later 3 plus. Thymol turbidity was 14.8 units, falling to 10.2. Electrocardiogram revealed no abnormalities. Complement fixation tests for histoplasmosis and coccidioidomycosis were negative. Skin testing with histoplasma antigen in dilutions of 1–100 and 1–1000, and with blastomycin and coccidiomycin gave negative findings. Intradermal injection of a Leishmania suspension resulted in the formation of a 2 mm. papule which persisted for forty-eight hours. (Table III.) The Frei test was negative. Liver aspiration revealed normal liver cells, except for fine granules faintly stained by hemotoxylin within the liver cells. Examination of the microscopic sections with the fluorescent microscope revealed strong fluorescence of the nuclei of the liver cells due to the presence of 2-hydroxystilbamidine. (Fig. 4.) On repeated x-rays of the clavicle progression in the periosteal reaction was seen without significant alteration in the area of destruction of the medial end. X-ray examination of the skull, dorsolumbar spine, pelvis, ribs, esophagus and chest revealed no abnormalities.

In view of the impressive improvement, 2-hydroxystilbamidine therapy was discontinued. The patient was maintained on a high caloric diet with parenteral vitamin therapy as well as chloromycetin for urinary tract infection. On this regimen the patient remained afebrile, her appetite continued excellent and in the middle of August, nearly three months after admission, the patient had gained a total of 36 pounds. The skin wound at the anterior chest had progressively decreased in size and had completely granulated and epithelialized. (Fig. 3.) The sequestrum of the clavicle was spontaneously extruded on August 4th. Pathologic examination revealed a bony sequestrum with acute osteomyelitis. During July and August it was noted on several occasions that the patient had several firm, non-pruritic, erythematous papules involving the upper extremities and thighs, which were discrete, well circumscribed and of evanescent character. Her blood count progressively rose to 13.5 gm. of hemoglobin, 4.35 million red blood cells, 4,500 white blood cells, with a persistent neutropenia with 35 per cent segmented forms, 62 per cent lymphocytes and 2 per cent monocytes; platelets 120,000. The sedimentation rate fell to 12–15 mm. in one hour and remained at these levels. Examination revealed both liver and spleen to have decreased in size, the former to one fingerbreadth below the costal margin and the latter to three fingerbreadths below the costal margin. The urinary tract infection was adequately managed with chloromycetin therapy. It was complicated by

the development of trichomonas vaginitis, which responded to vioform vaginal suppositories and instillation of vinegar douches. The patient was discharged three months after admission.

In April 1952, eight months after discharge, the patient was completely well. She looked excellent. There was a large smooth scar over the anterior chest. The liver and spleen were not palpable. The blood picture and the blood proteins were completely normal. (Fig. 1.)

COMMENTS

Leishmaniasis in South America occurs in three forms:[1] (1) Cutaneous leishmaniasis, comparable to the Aleppo boil of the Middle East; (2) South American mucocutaneous leishmaniasis; (3) visceral leishmaniasis, comparable to kala-azar and until now mainly found in Brazil.

Cutaneous leishmaniasis is a self-limited disease which usually heals within one year.

South American mucocutaneous leishmaniasis is a much more serious disease.[2] Its presence must be suspected in any patient who for some time has lived in the jungles of South America and who is suffering from ulcerations of skin and mucous membranes. This disease is widespread in nearly all South American countries and is said to be absent only in Chile and Patagonia. It is especially frequent in Brazil, Peru, Paraguay and Bolivia and it is known in different countries under different names, such as Espundia (in the Peruvian forests), Uta (Peruvian Andes), Bubas (Brazil), Chiclero ulcerations of the ears (Brazil and Guatemala), Pian de bois (French Guiana), bosch yaws or forest yaws (Dutch and British Guiana). An excellent review article of this disease published by Fox is generally used by American writers on the subject.[3] The disease presents itself as large ulcerations, often multiple, nearly always localized on the exposed parts of the body.[4,5] The ulcers increase gradually in size and in later stages are covered by thick crusts. Later the destruction of soft parts and cartilage, especially of the nose, sometimes even destruction of the hard palate, sets in. Secondary infection, fever, anemia, difficulty in swallowing result in cachexia and death. Occasionally there is an interval of more than one year between the development of the lesions of the skin and those of the mucous membranes. The latter may even develop after the skin lesions are healed.

Leishmaniasis of the mucous membranes usually starts on the anterior third of the nasal septum; thereafter pharynx, larynx, tongue and buccal mucosa become involved. There is little tendency to spontaneous healing. The organism can be demonstrated in the tissue as Leishman-Donovan bodies. When cultured in N.N.N. medium, Leishmanias present as flagellates. Unfortunately, as soon as secondary infection has set in, both these methods usually fail and the skin reaction of Montenegro has to be used.[6] For this reaction macerates of flagellates suspended in sodium chloride 0.9 per cent are injected intradermally. In cases of leishmaniasis, a red papule results after 24 and 48 hours.

Like all forms of leishmaniasis, the mucocutaneous syndrome is transmitted by the bite of a phlebotomus.[8]

Treatment with antimonials—especially fuadin—has been successful in many cases. However, the lesions of the mucous membranes are notoriously refractory to this treatment. The disease may last for many years and ultimately lead to death.

Very little is mentioned in the literature about changes of the peripheral blood, bone marrow and visceral organs. Here and there it is mentioned that leukopenia and thrombopenia occur. Splenic enlargement and hyperglobulinemia are not discussed.

Extensive investigations by the Chagas committee[9] have proved the existence of South American visceral leishmaniasis, comparable to the kala-azar of the Orient. In this form of the disease splenic and liver enlargement, leukopenia and hyperglobulinemia are found. Leishman-Donovan bodies can be demonstrated in the spleen, sometimes in the liver and in smaller quantities in the bone marrow. Here, too, antimonials have a curative influence.

As far as the diagnosis of our patient is concerned: (1) She had been in the jungle of an endemic area in South America. (2) The initial lesions involved the skin and were followed by lesions in the nose (boils), mouth, pharynx and larynx. (3) Many of the skin lesions healed either spontaneously or under the influence of one of the many therapeutic methods which were applied. When the patient arrived in New York, most of the skin and mucous membrane lesions had disappeared and were present only in the form of scars. The outstanding lesion was the large noma-like necrotic area over the left anterior chest. At the same time osteomyelitis of the clavicle was found. This was probably not due to leishmaniasis but may well have been the

result of the severe secondary infection of the skin. (4) The patient had extreme leukopenia, splenomegaly and hyperglobulinemia at admission. It is difficult to decide whether this was caused by the leishmaniasis or by the secondary infection of the gangrenous ulceration. She probably had thrombopenia during her stay in Colombia. (5) Leishman-Donovan bodies were found only in smears of the ulcer. They were not seen in sections of the ulcer margin or in bone marrow smears. No flagellates grew out in cultures made from the subcutaneous layers below the ulcer. (6) Skin reaction for leishmaniasis was positive and was negative for blastomyces, histoplasma and coccidiomyces. Syphilis and tuberculosis could be excluded. Blastomyces was not found either in sections or in cultures. In addition, the lesions did not have the character of blastomycosis.

In view of the presence of Leishman-Donovan bodies in the smears of the ulcer the diagnosis of American mucocutaneous leishmaniasis seems certain. Leukopenia and thrombopenia have been reported in this disease but splenomegaly must be very rare. Since no Leishman-Donovan bodies were found in the bone marrow, the diagnosis of a simultaneous infection with kala-azar is less probable, but this coincidence is not completely excluded.

The patient was treated with 2-hydroxystilbamidine di-isethionate, a derivative of stilbamidine or diamidino stilbene. After a total of 6.1 gm. had been given in the course of six weeks the following observations were made: (1) The anterior chest wound had decreased in size and was satisfactorily granulating. (2) The osteomyelitic process in the clavicle was associated with sequestrum formation. (3) The white blood cells had risen but there was still an associated neutropenia and the thrombocytes had fallen since admission. (Fig. 1.) (4) The patient, who on admission was in critical condition, had generally and significantly improved, having gained weight and become ambulatory and afebrile. (5) The spleen had remained essentially unchanged in size. The liver, which had previously not been palpated, was now noted four fingerbreadths below the costal margin. (6) The hyperglobulinemia manifest on admission had disappeared.

Two and a half months after the treatment was started, a complete cure was obtained and the patient was discharged from the hospital. Eight months later she was still completely well. Spleen and liver could not be palpated any more. The total blood count was normal. The ulceration of the chest wall had left a large scar which, as is usually the case in mucocutaneous leishmaniasis, is remarkably soft and pliable.

Stilbamidine and pentamidine have been employed successfully since 1939 for the treatment of kala-azar. These compounds have proved to be effective even in patients who had been refractory to antimony treatment.[10] (In order to avoid confusion it should be stressed that neither stilbamidine nor pentamidine contains antimony.)

Stilbamidine is injected intravenously in the form of stilbamidine di-isethionate containing 54 per cent of stilbamidine. An average of fifteen to twenty daily doses of 100 to 150 mg. are given. Pentamidine is administered intramuscularly as the hydrochloride salt in doses of 100 mg. Patients, especially women, have a tendency to develop hypotension after intravenous injections of stilbamidine but this can be avoided if a slow intravenous drip is used. But, apart from transient hypotension, stilbamidine has other unfortunate side effects. Two to three months after institution of stilbamidine treatment a dissociated neuropathy of the trigeminal area may develop.[16–19] This consists of anesthesia to touch in one or all of the branches of the trigeminal nerve, but without loss of pain or heat sensation. Subjectively, the patients complain of a "wooden" face, usually associated with tingling and burning, which is especially troublesome when it affects the eyelids and the forehead. These disagreeable paresthesias develop after a few months, even if the total dose of stilbamidine has not exceeded ten injections of 150 mg. In general, it appears that the larger the total dose given the more intense the trigeminal disturbance. In many patients the paresthesias persist for months, in exceptional cases even for years. This neuropathy is so disabling that stilbamidine has been replaced by pentamidine in the treatment of kala-azar, although the latter preparation is less potent than stilbamidine. In addition, stilbamidine has a deleterious effect upon the damaged kidney. Whereas stilbamidine has no adverse influence upon the function of the normal kidney, in myeloma patients with initial stages of uremia stilbamidine often has led to rapid deterioration and severe uremia.[15,17,18] Pentamidine frequently causes mental depression, drowsiness and forgetfulness.

Since the diamidines have considerable therapeutic possibilities, it seemed of importance to search for stilbamidine derivatives which would not deteriorate the function of a previously damaged kidney and especially not cause the very annoying trigeminal neuropathy. One of the stilbamidine derivatives, 2-hydroxystilbamidine, fulfills these requirements. Although it had already been established from animal experiments that this 2-hydroxy derivative, just like stilbamidine, destroys kala-azar flagellates in the test tube and in the experimental animal[22] the 2-hydroxy compound had never been used in humans.

We could demonstrate that after administration of 2-hydroxystilbamidine to myeloma patients, no trigeminal neuropathy developed.[23] A possible explanation for the latter difference may be connected with the light sensitivity of stilbamidine. Stilbamidine is changed under influence of ultraviolet light to a toxic compound. When exposed to the sunlight a stilbamidine solution readily loses its fluorescence whereas under the same conditions 2-hydroxystilbamidine hardly changes.[24] Certain actions of stilbamidine—for instance, inhibition of cholinesterase—disappear after irradiation with ultraviolet light whereas the anticholinesterase action of 2-hydroxystilbamidine changes much less. It thus seems possible that stilbamidine deposited in the skin under influence of sunlight slowly changes to a toxic substance and that the latter product causes the trigeminal neuropathy. In this connection it should be mentioned that in this part of the world the neuropathy is limited to the trigeminal areas. In the tropics, where the arms and chest are usually uncovered, these areas also are often involved.[19]

The leishmanicidal, bactericidal and fungicidal actions of 2-hydroxystilbamidine and of stilbamidine[11,12] are nearly identical. Both compounds inhibit the action of cholinesterase. After our observations on the absence of neurologic sequelae following administration of 2-hydroxystilbamidine had been reported, this compound was used successfully by Sen Gupta for the treatment of visceral kala-azar in India.[26]

Chemical determinations have proved that after stilbamidine or 2-hydroxystilbamidine injections considerable quantities of the diamidines can be found in different organs. Only 10 per cent of the diamidines injected is excreted in the urine.[20] The rest is deposited in various organs, especially in liver, kidneys and adrenals, and remains there for many months, even years.[21] This deposition varies to a certain extent in different species. In humans the diamidine concentration is highest in liver and adrenals, less in kidneys. It is also present in the sweat glands. In the mouse the largest concentration is found in the kidneys.

Whereas stilbamidine can be found in the cytoplasm of cells, combined with ribonucleic acid, in microscopic sections considerable quantities of 2-hydroxystilbamidine can be visualized, combined with the desoxyribonucleic acid of the nuclei and of the parenchymatous organs.[21,25] (Fig. 4.) It has not been decided yet whether deposition of 2-hydroxystilbamidine in the nuclei actually occurs *in vivo*. It is still possible that conjugation of the 2-hydroxy compound with the desoxyribose nucleic acid of the nuclei takes place only after fixation of the cells.

A biologic competition exists between arginine and either stilbamidine or 2-hydroxystilbamidine. This can be understood because structurally the diamidines and arginines show a certain similarity. The bactericidal and fungicidal actions of stilbamidine, 2-hydroxystilbamidine, pentamidine and propamidine are neutralized by addition of arginine.[24] The anticholinesterase action of the diamidines is also neutralized by arginine.

Whereas 2.5 gm. of stilbamidine almost always causes severe trigeminal neuropathy, after 6.1 gm. of the 2-hydroxy compound our patient did not suffer any discomfort in the area of the fifth nerve. As mentioned previously the 2-hydroxystilbamidine treatment of patients with multiple myeloma also did not lead to any trigeminal complaints. The same freedom from trigeminal paresthesias was observed in three patients with extensive blastomycosis.[27] One of these patients needed more than 15 gm. of 2-hydroxystilbamidine before complete healing was obtained.

During the second series of injections thrombopenia and liver swelling developed in our patient with leishmaniasis. We have never observed these complications either in patients with myeloma or blastomycosis who were treated with 2-hydroxystilbamidine. It should be remembered that the patient with leishmaniasis had already suffered from thrombopenia while she was still in Colombia. During the treatment of kala-azar with antimonials, increase of thrombopenia and hepatomegaly is frequently observed and in view of our observations in

other diseases we are therefore inclined to ascribe these signs more to the leishmaniasis than to the medication.

SUMMARY

A protracted and stormy illness in a young American woman, contracted after a prolonged sojourn in the jungle areas of Ecuador, was characterized by fever, chills, mucocutaneous ulcerations and gangrenous ulceration of the chest wall. Treatment with many antibiotics and finally radiotherapy were without effect on the fever, local lesions or general condition. On admission the patient was critically ill, with fever, noma-like gangrene of the chest wall, osteomyelitis of the clavicle, splenomegaly, leukopenia, granulocytopenia and hyperglobulinemia.

Smears from the ulcer surface demonstrated the presence of Leishman-Donovan bodies but bone marrow smears were negative. Montenegros test for leishmaniasis was positive.

The diagnosis of American mucocutaneous leishmaniasis was made and the patient treated with 2-hydroxystilbamidine to a total of 6.1 gm., with remarkable recovery. The gangrene healed completely, and after spontaneous extrusion of a small sequestrum the osteomyelitis of the clavicle healed, leaving a soft pliable scar. Splenomegaly disappeared and the total blood count and serum globulin returned to normal.

It is emphasized that 2-hydroxystilbamidine has the same leishmanicidal action as stilbamidine but that the disagreeable side actions of stilbamidine—trigeminal neuropathy and renal toxicity—are not caused by the 2-hydroxy compound.

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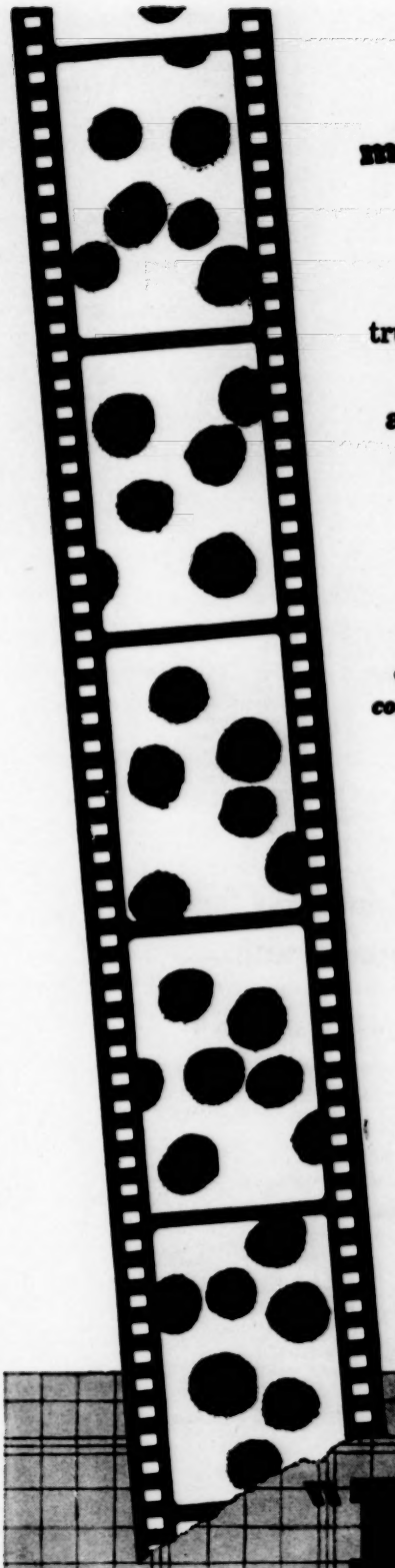

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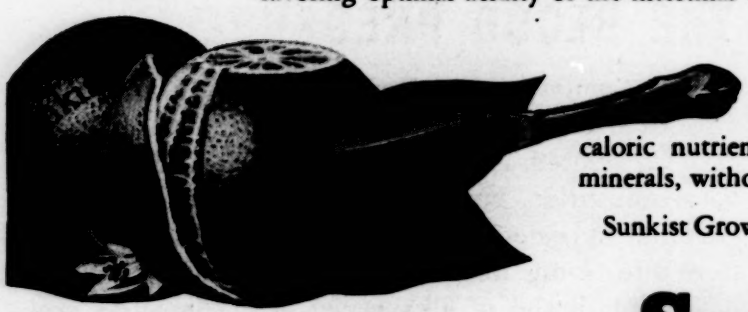

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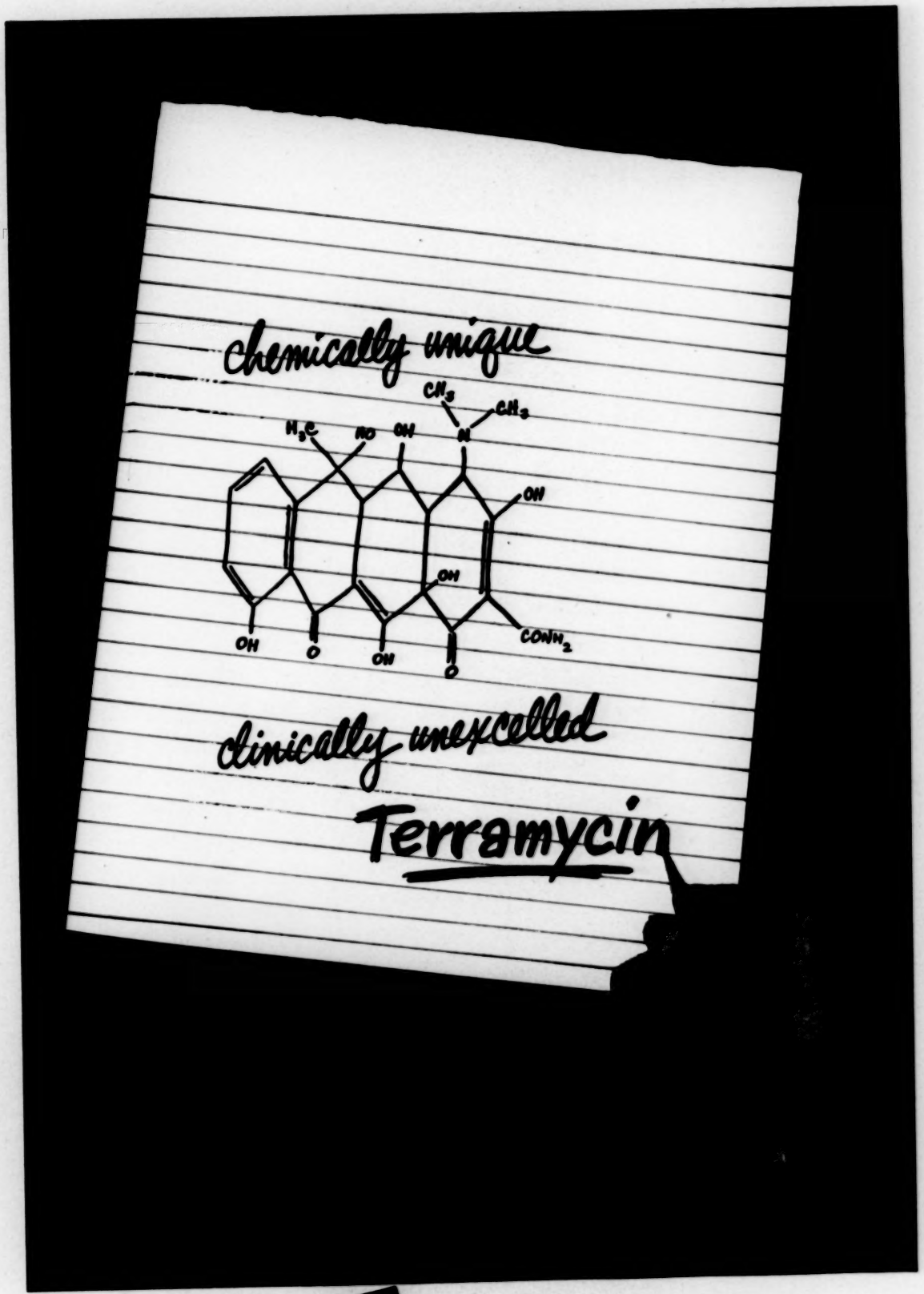

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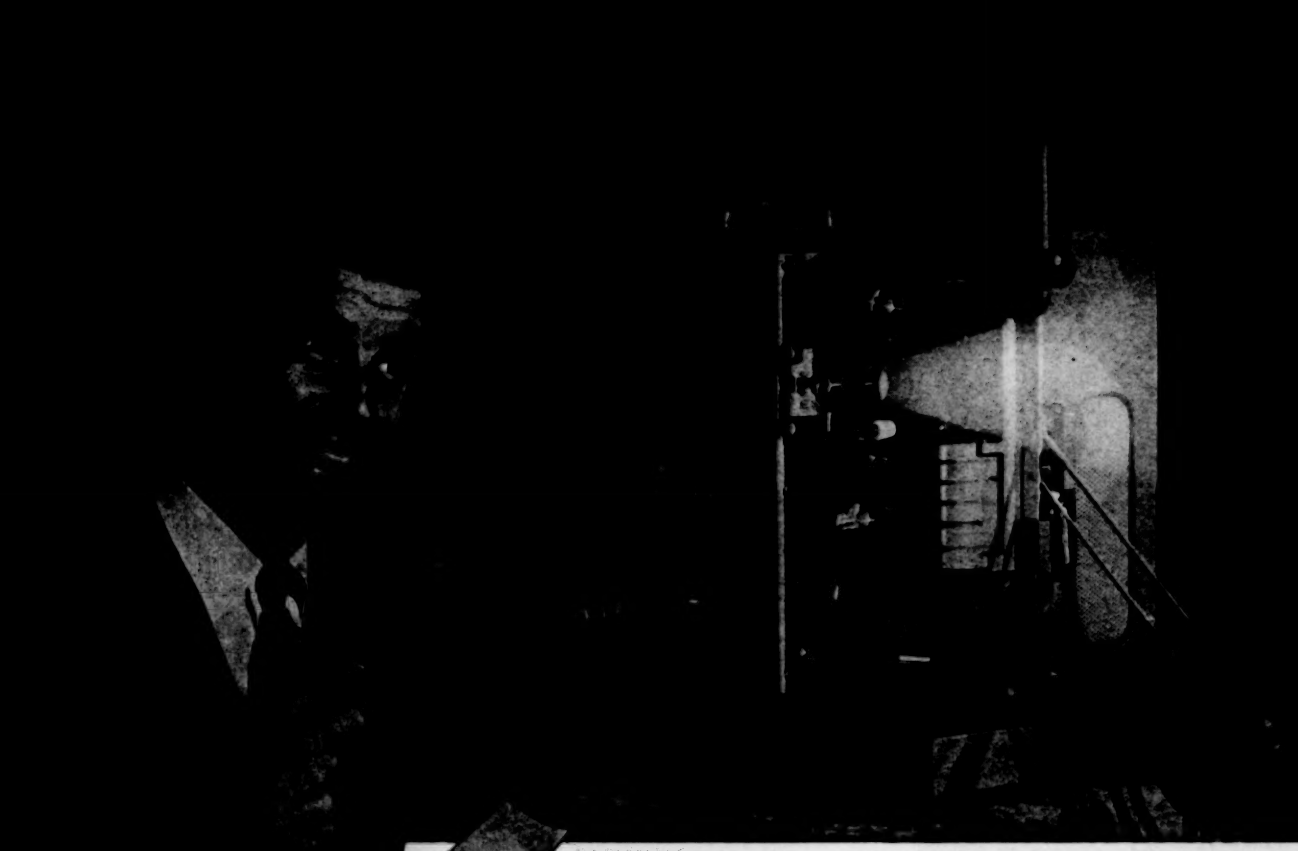

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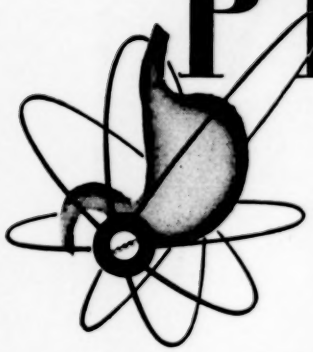

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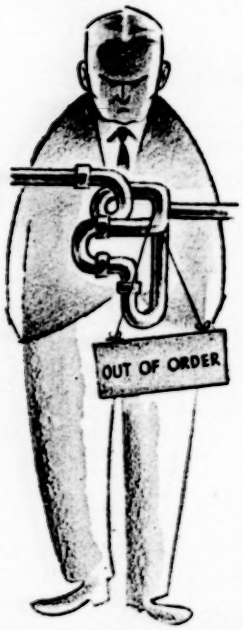

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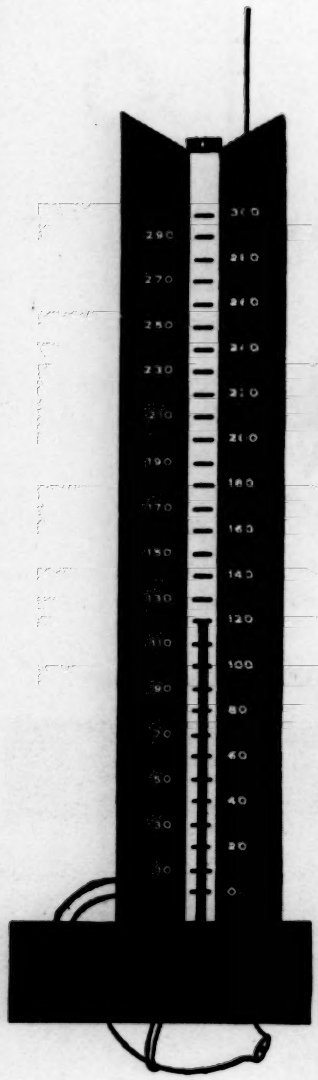

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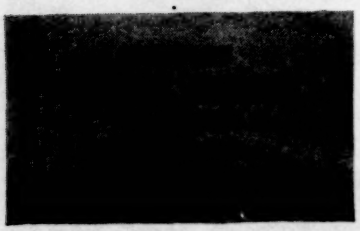

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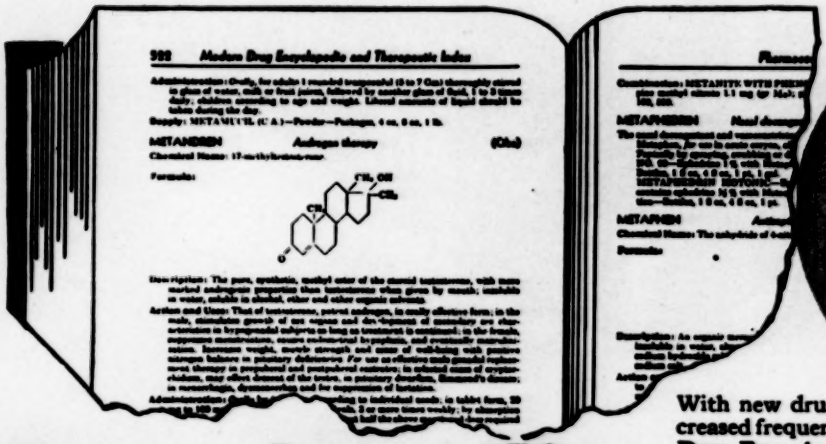

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for Control of Hypertension

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Effective in essential hypertension with relatively fixed levels, early malignant hypertension, toxemias of pregnancy, and acute glomerulonephritis.

Induces gradual and sustained reduction of blood pressure with no dangerous, abrupt fall on oral administration.

Affords uniform rate of absorption and marked antihypertensive effectiveness.

Increases renal plasma flow in marked contrast to the decrease associated with other hypotensive drugs.

Produces significant relaxation of cerebral vascular tone without decrease in cerebral blood flow.

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Complete information regarding manner of use and clinical application available on request.

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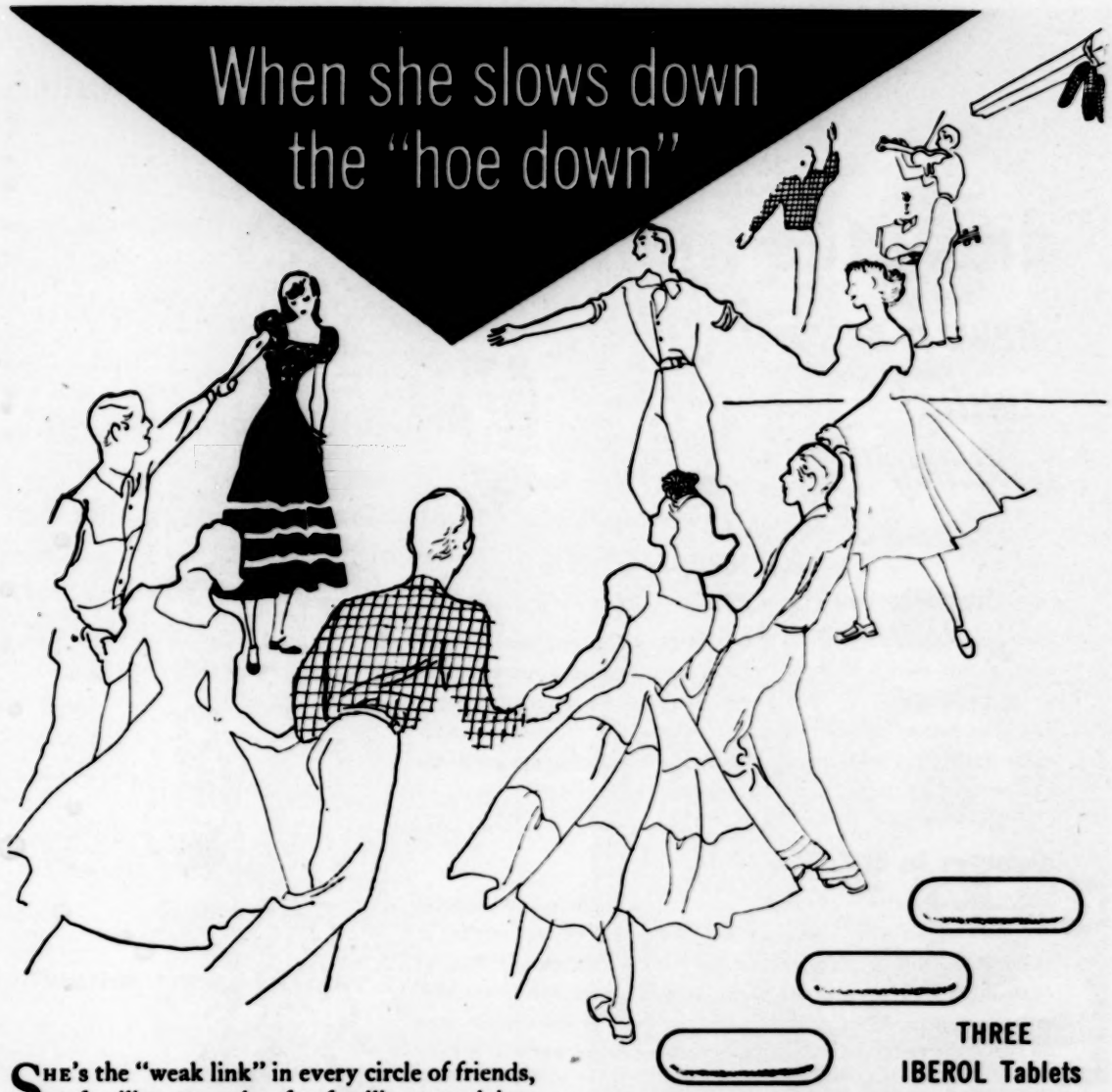
When she slows down the "hoe down"



SHE's the "weak link" in every circle of friends, a familiar example of a familiar complaint: hypochromic microcytic anemia. And it's a good bet that other nutritional deficiencies are contributing to her general debility.

The IBEROL formula points up three significant advantages in such cases: (1) *Just three tablets a day* provide a full therapeutic dose of iron (2) *Other blood-building elements*—including the B complex factors and standardized stomach-liver digest—are present to hasten recovery and furnish a wider range of therapy. (3) *Potency* is combined with *compactness* to assure ease and economy of treatment.

For prophylaxis in pregnancy, old age, and convalescence, one or two tablets a day are usually sufficient. At pharmacies in bottles of 100, 500, and 1000. Abbott

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the average daily therapeutic dose for adults, supply:

Ferrous Sulfate	1.05 Gm.

(representing 210 mg. elemental iron, the active ingredient for the increase of hemoglobin in the treatment of iron-deficiency anemia)

Plus these nutritional constituents:

Thiamine Mononitrate (6 times MDR*)	6 mg.
Riboflavin (3 times MDR*)	6 mg.
Nicotinamide (2 times RDA†)	30 mg.
Ascorbic Acid (5 times MDR*)	150 mg.
Pyridoxine Hydrochloride	3 mg.
Pantothenic Acid	6 mg.
Vitamin B_{12}	30 mcg.
Folic Acid	3.6 mg.
Stomach-Liver Digest	1.5 Gm.

*MDR—Minimum Daily Requirement
†RDA—Recommended Daily Dietary Allowance

Specify

Iberol® tablets

(Iron, B_{12}, Folic Acid, Stomach-Liver Digest, with Other Vitamins, Abbott)

"diabetes mellitus *shows a marked familial tendency"*[1]

the diabetic family

Every case of diabetes is a clear indication to test the patient's relatives for evidence of the "pronounced inherited susceptibility to the development of the clinical form of the disease."[1] Early diagnosis makes possible the early control and continuous treatment that are "of the greatest importance in reducing the incidence and severity of degenerative complications."[2]

diabetes in children

Testing for diabetes is especially indicated in children and youthful members of diabetic families, since "the age at onset is earlier in those cases with positive family histories of diabetes."[1] Prompt control is a significant factor in postponing or preventing vascular complications—now responsible for more deaths and debility than all other causes in patients with onset of diabetes early in life.[2]

CLINITEST

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for urine-sugar detection

Detection of urine-sugar is simple, reliable and rapid with *Clinitest* (Brand) Reagent Tablets. The results are directly read. No external heating is needed. *Clinitest* is excellent for office and clinic, and for diabetic patients.

1. Watson, E. M., and Thompson, M. W.: Am. J. Digest. Dis. *18*:326, 1951.

2. Wilson, J. L.; Root, H. F., and Marble, A.: J.A.M.A. *147*:1526 (Dec. 15) 1951.

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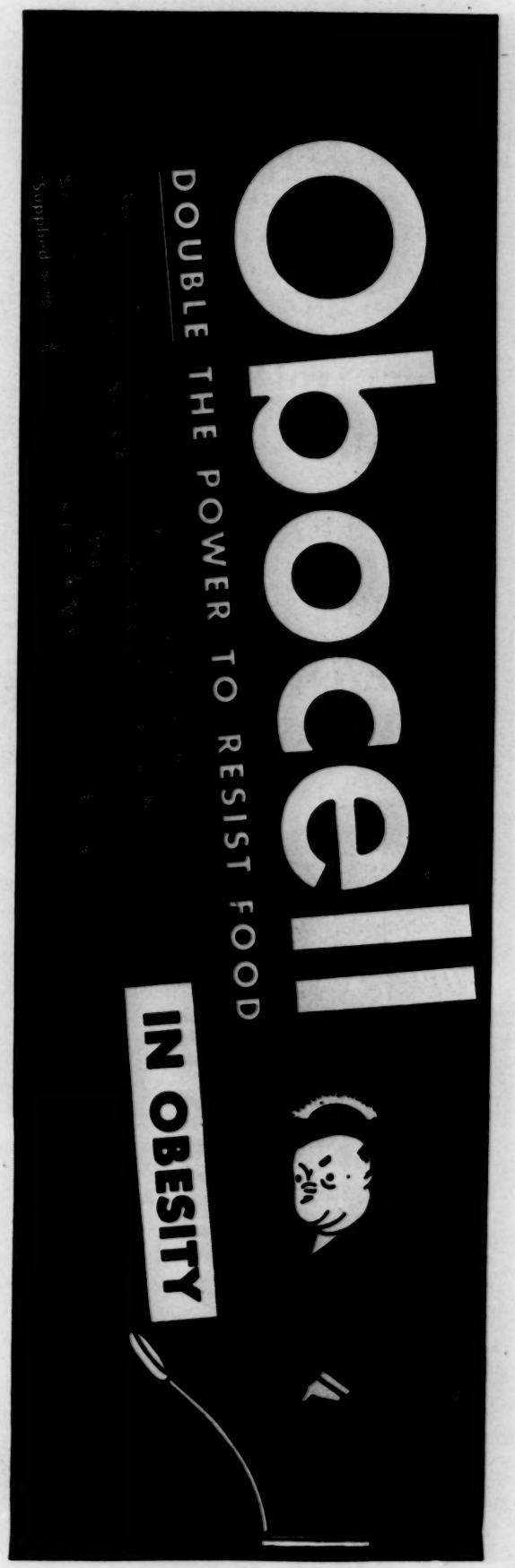
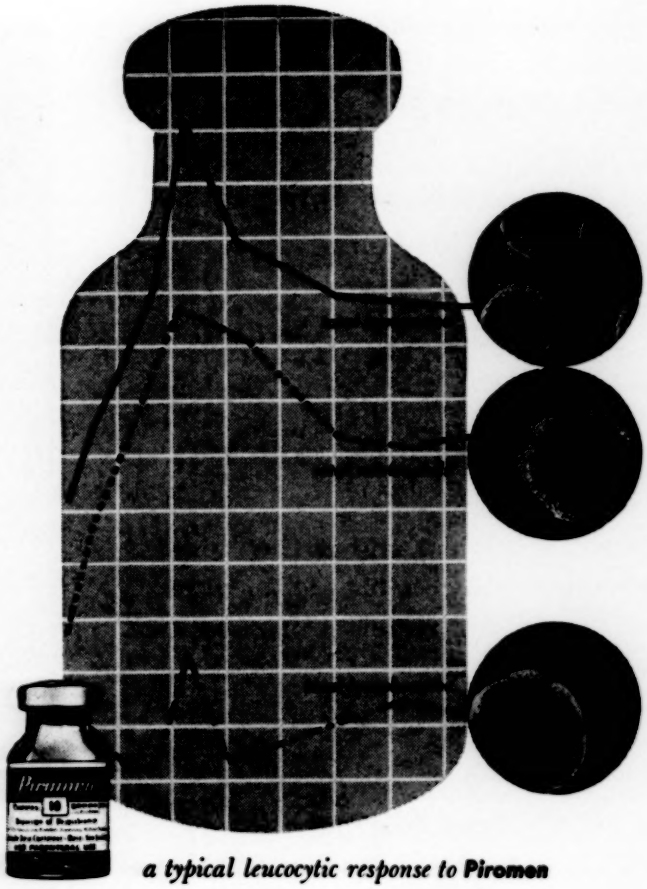


Piromen*

(DISPERSION OF DESACCHROMIN)

for effective control of a wide variety of *ALLERGIES* and *DERMATOSES*



a typical leucocytic response to **Piromen**

Every day more physicians are discovering the early clinical benefits effected by the administration of ***Piromen,*** employed either as a specific, or concomitantly with other drugs.

Piromen is a biologically-active bacterial polysaccharide which produces a marked leucocytosis and a stimulation of the reticulo-endothelial system. It is nonprotein, nonantigenic, and may be employed safely within a wide range of dosage.

Piromen is prepared in stable colloidal dispersion for parenteral use. It is supplied in 10 cc. vials containing either 4 gamma (micrograms) per cc., or 10 gamma per cc.

For a comprehensive booklet detailing the use of this new therapeutic agent, merely write "***Piromen***" on your *Rx* and mail to—

*TRADE MARK

Manufactured by

TRAVENOL LABORATORIES, INC.

Subsidiary of BAXTER LABORATORIES, INC., MORTON GROVE, ILLINOIS

by living test

Motility recordings from the small intestine by the multiple-balloon intubation technic[1] — plus controlled clinical observations have demonstrated the superiority of natural belladonna alkaloids as in Donnatal over atropine alone and over the newer synthetics, in relieving smooth muscle spasm with minimal side-effects.

Each tablet, each capsule and each 5 cc. (1 teaspoonful) of elixir contains hyoscyamine sulfate 0.1037 mg., atropine sulfate 0.0194 mg., hyoscine hydrobromide 0.0065 mg. and phenobarbital ½ gr. (16.2 mg.).

[illegible] 12:1227, 1938.

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Ethical Pharmaceuticals
of Merit since 1878

onnatal

Question:

WHAT MAKES Biphetacel SUPERIOR?

Answer:

THE EXCLUSIVE 1:3 L/D RATIO!

"IN CURBING APPETITE and causing weight loss, a combination of Monobasic amphetamine phosphate containing a ratio of 1:3 of levo to dextro amphetamine (as found exclusively in Biphetacel) is more effective than the same amount of amphetamine contained in the racemic form where the ratio is 1:1 l/d . . ."*

Because of its exclusive 1:3 l/d ratio, Biphetacel curbs appetite more effectively, without nausea or nervousness, in both vagotonic or "sluggish" and sympathicotonic or "high strung" patients. In addition, it preserves an "enough-to-eat" feeling by decreasing gastric motility and prolonging emptying time of stomach, and assures normal elimination by supplying evenly distributed, non-nutritive, "no clump" bulk. Small dosage means low treatment cost.

Each Biphetacel tablet contains the preferred 1:3 l/d ratio as provided by Racemic Amphetamine Phosphate Monobasic 5 mg. and Dextro Amphetamine Phosphate Monobasic 5 mg.; Metropine® (methyl atropine nitrate, Strasenburgh) 1 mg., Sodium Carboxymethylcellulose 200 mg.

Dosage: 1 tablet ½ hour before meals, three times daily, for the vagotonic type. Increase this dose, if necessary, to achieve the desired clinical results. ½ tablet ½ hour before meals, three times daily, for one week for the sympathicotonic type. If no signs of intolerance develop, increase to 1 tablet. Supplied in bottles of 100 and 1000 scored tablets.

For literature and supply for initiating treatment, write Medical Service Department, R. J. Strasenburgh Co., Rochester 14, N. Y.

*Freed, S. C. and Mizel, M.—in press

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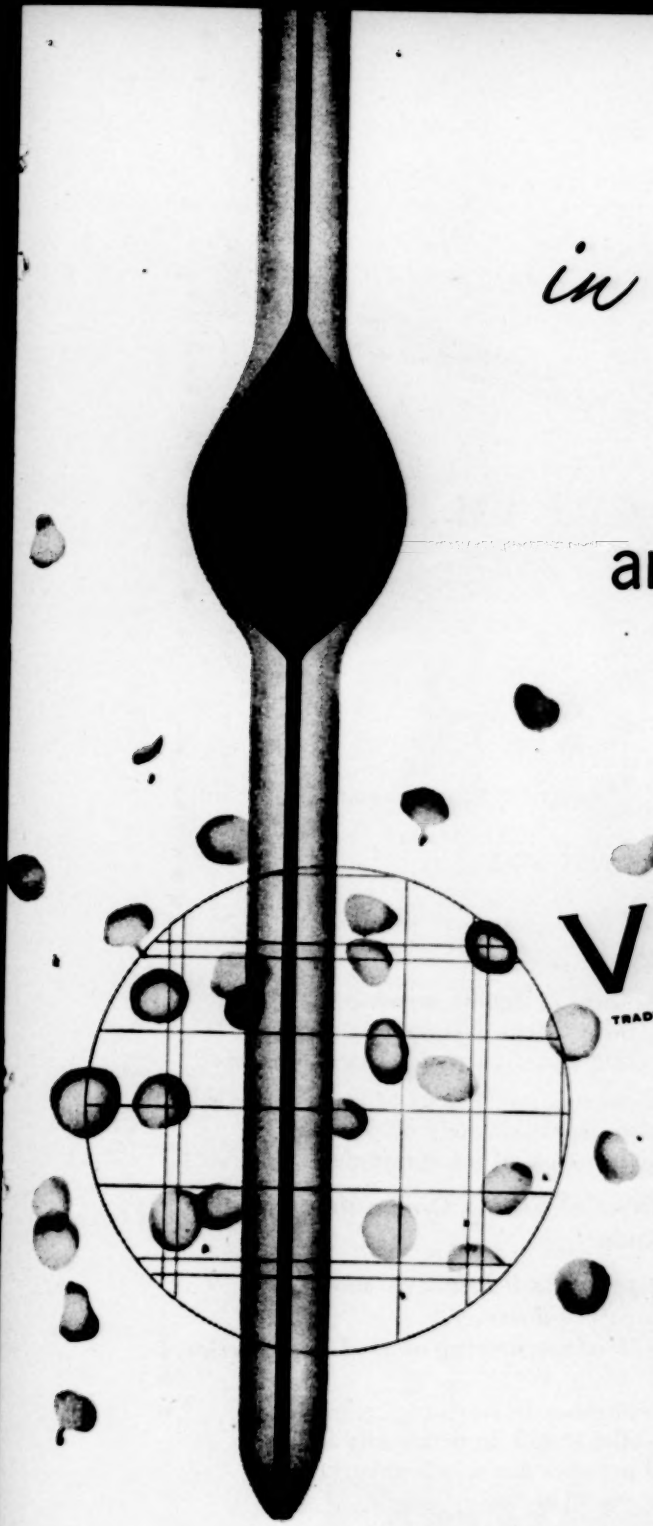
"Eat Less and Like It!"

Strasenburgh

FOUNDED IN 1886



in anemia . . .

to brighten the color

and raise

the count

VENTRILEX
KAPSEALS®

TRADE MARK

EACH VENTRILEX KAPSEAL CONTAINS:

Crystalline Vitamin B_{12}	20 micrograms
Liver Concentrate	0.1 Gm.
Ferrous Sulfate	0.2 Gm.
Concentrated Extract of Stomach	0.3 Gm.
Folic Acid	2.0 mg.
Vitamin C	50.0 mg.

COMPREHENSIVE BLOOD THERAPY

Because they contain six basic factors essential to normal blood formation, VENTRILEX Kapseals assure comprehensive therapy in the anemias commonly encountered in daily practice. Reticulocyte response is rapid and hemoglobin regeneration prompt regardless of the type of anemia — macrocytic, normocytic or microcytic.

VENTRILEX Kapseals are also valuable as prophylactic therapy during pregnancy, in prolonged illness, in convalescence, and in the clinical management of geriatric patients.

MEDICAMENTA VERA

Parke, Davis & Company

DETROIT MICHIGAN

76.6% of patients preferred

EURAX® CREAM...

76.6%

for relief of pruritus

In a recent study[1] of 200 cases of itching dermatoses, 76.6% of all patients who had had previous experience with other antipruritics expressed a preference for EURAX Cream.

In this study, as in previous reports[2-5], EURAX Cream produced complete relief of itching in approximately 65 per cent of cases, and partial relief in most of the remainder.

Other favorable features of EURAX Cream that were again confirmed include:

✓ ***Prolonged effect lasting up to 8 hours or more.***
✓ ***No loss of effect on continued use.***
✓ ***Virtually complete lack of sensitizing or toxic properties.***

EURAX... not an antihistaminic or a -caine derivative... is indicated for prompt, prolonged relief of itch in practically all forms of dermatosis including pruritus due to administration of antibiotics.

EURAX Cream* (brand of crotamiton cream) contains 10% N-ethyl-o-crotonotoluide in a vanishing-cream base.
Tubes of 20 Gm. and 60 Gm. and jars of 1 lb. at your local pharmacy.

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1. Hitch, J. M.: North Carolina M. J. *12*:548, 1951.
2. Peck, S. M., and Michelfelder, T. J.: New York State J. Med. *50*:1934, 1950.
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4. Soifer, A.: Quart. Rev. Int. Med. & Dermat. *8*:1, 1951.
5. Johnson, S. M., and Bringe, J. W.: Arch. Dermat. & Syph. *63*:768, 1951.

*U.S. Pat. #2,505,681.

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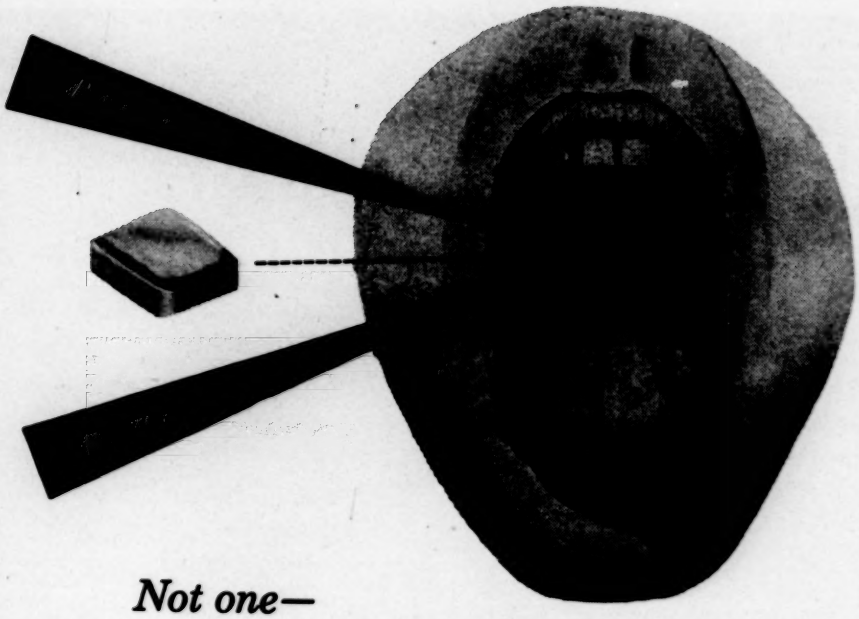

Not one—

but two—potent antibiotics

PONDETS, the delicious antibiotic troches that look and taste like candy, are active against a wide variety of pathogens commonly found in the mouth and throat.

Penicillin and Bacitracin, each highly effective when employed locally against infections of the mouth and pharynx, are especially effective when combined. Together, they exhibit marked synergism.[1,2]

PONDETS dissolve slowly, supplying an uninterrupted high concentration of each antibiotic to the infected oral and pharyngeal mucosa.

Pondets®

PENICILLIN · BACITRACIN TROCHES

Each PONDET contains 20,000 units crystalline potassium penicillin G and 50 units bacitracin. Vacuum-packed in tins of 48.

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1. Eagle, H., and Fleischman, R.: Proc. Soc. Exper. Biol. & Med. *68*:415 (June) 1948.

2. Bachman, M.C.: J. Clin. Invest. *28*:864 (Sept.) 1949.